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(54) Title: MULTIPLE ACTION COMPOUNDS

(57) Abstract: The present invention refers to novel multiple action compounds, that is, to compounds which contain at least two pharmaceutically active components in one molecule. The compounds have a higher stability than corresponding compounds of the prior art.

Multiple Action Compounds

The present invention refers to novel multiple action compounds, that is, to compounds which contain at least two pharmaceutically active components in one molecule.

The intensive use of pharmaceutically active compounds and especially of antibiotics has exerted a selective evolutionary pressure on microorganisms to produce genetically based resistance mechanisms. Further modern medicine and socio-economic behavior exacerbate the problem of resistance development by creating slow growth situations for pathogenic microbes, e.g. artificial joints-related infections, and by supporting long-term host reservoirs, e.g. in immuno-compromised patients.

In hospital settings, an increasing number of strains of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus sp.*, and *Pseudomonas aeruginosa*, major sources of infections, are becoming multi-drug resistant and therefore difficult if not impossible to treat.

- *S. aureus* is ß-lactam, quinolone and now even partly vancomycin resistant.
- *S. pneumoniae* is becoming resistant to penicillin and even to new macrolides.
- *Enteroccocci* are quinolone and vancomycin resistant and ß-lactams were never efficacious against these strains. The only alternative is to use oxazolidinone (e.g. linezolid) but this compound is not baetericidal. However even with linezolid, resistance already appears in clinical practice.

In addition, microorganisms that are causing persistent infections are increasingly being recognized as causative agents or cofactors of severe chronic diseases like peptic ulcers or heart diseases.

It is therefore an object of the present invention to provide pharmaceutically active compounds which show a higher activity than usual pharmaceutically active compounds.

It is a further object of the present invention to provide pharmaceutically active compounds which are stable under physiological conditions.

It is a still further object of the present invention to provide pharmaceutically active compounds which cause less resistance than usual compounds with a similar activity or which render the development of resistance more difficult.

It is still a further object of the present invention to provide pharmaceutically active compounds which have a better pharmacological profile (e.g. longer half-lifetime in the body).

These objects are solved according to the present invention by providing compounds which contain at least two pharmaceutically active components.

The compounds according to the present invention are compounds with multiple, especially dual pharmaceutical activities. The term "pharmaceutical activity" comprises any bioactivity of a compound or substance and such compounds or substances can be, e.g. therapeutically active, prophylactically active and/or pharmacologically or physiologically active substances with a beneficial activity for humans, animals or

plants. Most preferred it refers to therapeutical activity, beneficial for humans. Moreover, they can be used as well as disinfectants.

More specifically the present invention refers to a compound with at least two components each of which is capable of exerting a pharmaceutical activity, localized or systemic, irrespective of whether therapeutic, diagnostic or prophylactic in nature.

Such components preferably are each known medicaments from known medicament classes or classes of medicaments in clinical or preclinical trial or classes of medicaments under research or development or close analogues of them. Examples of such medicaments are disclosed in US Patent 5,656,286 of Noven Pharmaceuticals as printed in columns 11 to 32, which are incorporated herein by reference. Especially preferred are antiinfective components, especially antiviral, antifungal or antibacterial components.

Thus, under one aspect, the present invention refers to coupling of two or more known medicaments like antibiotics to form a chemical compound containing both or all of these medicaments.

The components are preferably linked in a manner known per se to a chemist or biochemist. For example, to generate a link, a substituent like a H (or any other)-atom or group like a known leaving group of each medicament (component) can be replaced by a covalent bond, a spacer etc. as disclosed in the present invention. Thus, two components can be linked by one bond, double bond etc., or one spacer etc. Moreover, two medicaments (components) etc. or parts thereof can be connected in a way that they share one (e.g. structural) element necessary for

their pharmaceutical activity. The links are preferably such that they - and especially preferred also the complete compounds - are stable under physiological conditions; at least until they reach the loci (targets) of their physiological action.

Physiological conditions per se are known in the art. They can differ according to the target or locus of the target. The term "physiological conditions" according to the present invention preferably refers to

- a pH-value in the range from 1 to 10, more preferably from 4 to 9, still more preferably from 6 to 8;

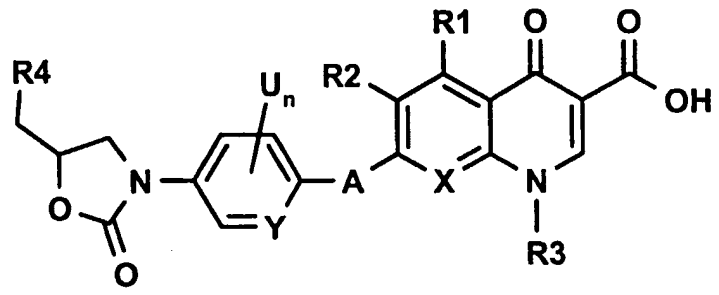
- a temperature in the range from 36 to 40 °C, more preferably in the range from 36,5 to 38 C and especially preferably from 36,7 to 37 °C;

- further conditions of the body, especially the blood, stomac or lung of mammals, especially humans.

The term "physiological conditions" most preferably refers to the conditions in the blood of healthy humans.

The term "stable" preferably refers to a degradation of less than 10% preferably less than 5% of the compounds of the present invention within at least 30 min preferably within at least 60 min, more preferably within at least 8 hours and especially preferred within at least 24 hours after administration in the blood of humans. That means that the stable links (covalent bonds, elements or spacers) and preferably also the complete compounds are stable, preferably in the human body or blood, for this period of time so that the compounds can exert their pharmaceutical activity.

Examples of the compounds of the present invention are compounds of Formula (I) that are, e.g., useful antimicrobial agents and effective against a variety of multi-drug resistant bacteria:



(I)

wherein A is a direct bond, a NH, O, S, SO, SO_2, SO_2NH, PO_4, -NH-CO-NH-, -CO-NH-, -CO-, -CO-O-, -NH-CO-O-, an alkylen group, a heteroalkylen group, an arylen group, a heteroarylen group, a cycloalkylen group, a heterocycloalkylen group, an alkylarylen group or a heteroarylalkylen group or a combination of two or more of these atoms or groups; X is CR5 or N; Y is CR6 or N; U is F or Cl; n is 0, 1, 2 or 3; R1 is H, F, Cl, Br, I, OH, NH_2, an alkyl group or a heteroalkyl group; R2 is H, F or Cl; R3 is H, an alkyl group, a heteroalkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an alkylaryl group or a heteroarylalkyl group all of which may be substituted with one, two or more halogen atoms like F or Cl; R4 is a heteroalkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an alkylaryl group or a heteroarylalkyl group; R5 is H, F, Cl, OH, NH_2, an alkyl group or a heteroalkyl group, or R3 and R5 can be linked via an alkylen or heteroalkylen group or be a part of a cycloalkylen or heterocyclo-alkylen group; in case R3 is no H and R5 is no H, F, OH, NH_2 or Cl; R6 is H, F, Cl or OMe or a pharmacologically acceptable salt, solvate, hydrate or formulation thereof.

Preferred are compounds of Formula (I), wherein R1 is H or NH_2.

Further preferred are compounds of Formula (I), wherein R2 is H or F.

Moreover preferred are compounds of Formula (I), wherein R3 is an ethyl, a 2-propyl, a C3-C6 cycloalkyl, a phenyl or a pyridyl group. All these groups may be substituted by one or more fluorine atoms or amino groups.

Moreover preferred are compounds of Formula (I), wherein R3 is a cyclopropyl group.

Further preferred are compounds of Formula (I), wherein R3 and R5 together form a bridge of the formula $-O-CH_2-N(Me)-$ or $-O-CH_2-CH(Me)-$. Herein, the preferred stereochemistry at the chiral center is the one giving the S configuration in the final compound.

Further preferred are compounds of Formula (I), wherein R4 is a group of the formula -NHCOCH=CHAryl, -OHeteroaryl (especially -oxa-3-oxazol), $-NHSO_2Me$, -NHCOOMe, $NHCS_2Me$, $NHCSNH_2$, -NHCSOMe or -NHCOMe.

Especially preferred are compounds of Formula (I), wherein R4 is an acetylamino group.

Moreover preferred are compounds of Formula (I), wherein R5 is H, F, Cl or a methoxy group which may be substituted by one, two or three fluorine atoms.

Further preferred are compounds of formula (I), wherein X is N or CH.

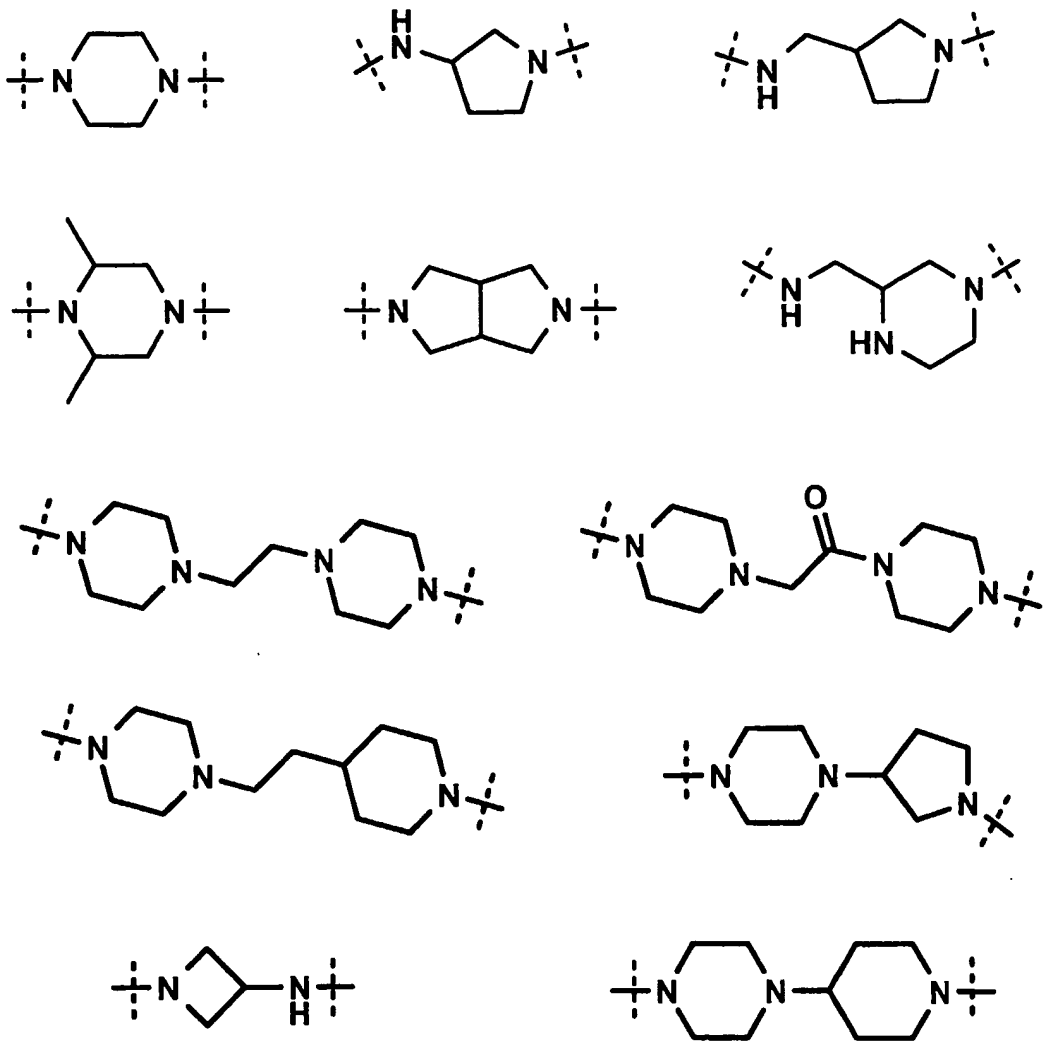
Further preferred are compounds of Formula (I), wherein Y is N or CF.

Further preferred are compounds of Formula (I), wherein n is 0.

Further preferred are compounds of Formula (I), wherein A is a bond.

Moreover preferred are compounds of Formula (I), wherein A is a cycloalkylen or a alkylcycloalkylen group that contains 2, 3 or 4 nitrogen atoms and may be substituted by one, two or more fluorine atoms and the nitrogen atoms may be substituted by an alkyl or an acyl group.

Further preferred are compounds of Formula (I), wherein A is selected from the following groups which may be further substituted by one, two or more fluorine atoms or by an alkyl group which may be substituted by one, two or more fluorine atoms, and wherein the amino groups may be substituted by an alkyl or an acyl group:



Further preferred are compounds of Formula (I), wherein the absolute configuration at C-5 of the oxazolidinone ring is (S) according to the Cahn-Ingold-Prelog nomenclature system.

The compounds according to the present invention have a higher stability than corresponding compounds of the prior art which are unstable under physiological conditions possibly causing the unwanted release of an active ingredient before the compounds reach their targets. Such prior art compounds specifically do not have the requested stability under physiological conditions.

If the at least two components are pharmaceutically active themselves, they maintain their activity when combined to one molecule, if either one of the components is not pharmaceutically active before, it becomes pharmaceutically active when combined with another component to one compound according to the present invention. Accordingly, all components according to the present invention, that is, when incorporated into one molecule, are pharmaceutically active.

A pharmaceutically active component is e.g. a chemical scaffold like a hydrocarbon chain or a hydrocarbon ring carrying at least one pharmacophore. "Pharmacophore" is a commonly used term in the art and is defined as containing at least one functional group which is oriented in space in a specific manner and is responsible for a biological activity. Such pharmacophores are, e.g., described in Böhm, Hans-Joachim, et al., Wirkstoffdesign, Heidelberg; Berlin; Oxford; Spektrum, Akad. Verl., 1996.

The Multiple Action Compounds of the present invention can have one or more of the following modes of action:

- At least two components have pharmaceutical activities;

- One component can act as the actual active ingredient while another component can inhibit enzymes etc. which can degrade the active ingredient or inhibit its action;

- At least two components can act as inhibitors in the same biological pathway or in different pathways. In both cases synergy may occur;

- One component releases a second component after having exerted its own pharmaceutical role.

A further advantage of the compounds of the present invention is due to the fact that multiple diseases can be cured with one compound (medicament) so that the comfort and compliance of the patients is largely increased. This is especially important when different pathogenic bacteria have to be treated with different antibiotics. Moreover, the problem of resistance development is minimized.

According to one embodiment of the present invention the compounds of the present invention can contain at least two components which share one (structural) element. In this case the at least two components share one element like a phenyl ring, which is - contrary to a spacer -necessary for the activity of the at least two components. The at least two, preferably two, components contain preferably only one such element. In other words, at least two components or pharmacophores can be forged into one compound according to the present invention, which is preferably stable under physiological conditions.

According to a further embodiment of the present invention the compounds of the present invention can contain at least two components which are connected with a covalent bond which is preferably stable under physiological conditions.

According to a further embodiment of the present invention the compounds of the present invention can contain at least two components which are linked (connected) with a spacer. The term "spacer" is per se known in the art. According to the present invention a spacer is any chemical element or group capable of

linking the at least two pharmaceutically active components of the present invention and can e.g. be a -NH, -O-, -S-, -SO-, -SO_2-, -SO_2NH-, -PO_4-, -NH-CO-NH-, -CO-NH-, -CO-,-CO-O- -NH-CO-O- group, an alkylene group, a heteroalkylene group, an arylene group, a heteroarylene group, a cycloalkylene group, a heterocycloalkylene group, an alkylarylene group or a heteroarylalkylene group. Such links are preferably stable under physiological conditions.

The term alkyl refers to a saturated or unsaturated (i.e. alkenyl and alkinyl having one, two or more double and/or triple bonds) straight or branched chain alkyl group, containing from one to ten, preferably one to six carbon atoms for example methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl n-hexyl, 2,2-dimethylbutyl, n-octyl; ethenyl (vinyl), propenyl (allyl), iso-propenyl, n-pentyl, butenyl, isoprenyl or hexa-2-enyl; ethinyl, propinyl or butinyl groups. Any alkyl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, NH_2, OH, SH or NO_2.

The term heteroalkyl refers to an alkyl group as defined herein where one or more carbon atoms are replaced by an oxygen, nitrogen, phosphorous or sulphur atom for example an alkoxy group such as methoxy, ethoxy, propoxy, iso-propoxy, butoxy or tert.-butoxy, an alkoxyalkyl group such as methoxymethyl, ethoxymethyl, 1-methoxyethyl, 1-ethoxyethyl, 2-methoxyethyl or 2-ethoxyethyl, an alkylamino group such as methylamino, ethylamino, propylamino, isopropylamino, dimethylamino or diethylamino, an alkylthio group such as methylthio, ethylthio or isopropylthio or a cyano group. The term heteroalkyl furthermore refers to a group derived from a carboxylic acid or carboxylic acid amide such as acetyl, propionyl, acetyloxy,

propionyloxy, acetylamino or propionylamino, a carboxyalkyl group such as carboxymethyl, carboxyethyl or carboxypropyl, a carboxyalkyl ester, an alkylthiocarboxyamino group, an alkoxyimino group, an alkylaminothiocarboxyamino group or an alkoxycarbonylamino group. Any heteroalkyl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, NH_2, OH, SH or NO_2.

The term cycloalkyl refers to a saturated or unsaturated (having one, two or more double and/or triple bonds), cyclic group with one, two or more rings, having three to 14 ring-carbon atoms, preferably from five or six to ten ring-carbon atoms, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetralin, cyclopentenyl or cyclohex-2-enyl groups. Any cycloalkyl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, OH, NH_2, SH, N_3, NO_2, alkyl groups such as methyl or ethyl, heteroalkyl groups such as methoxy, methylamino, dimethylamino or cyanide.

The term heterocycloalkyl refers to a cycloalkyl group as defined herein where one, two or more ring-carbon atoms are replaced by one or more oxygen, nitrogen, phosphorous or sulphur atoms for example piperidino, morpholino or piperazino groups.

The term aryl refers to an aromatic cyclic group with one or more rings, having five to 14 ring-carbon atoms, preferably from five or six to ten ring-carbon atoms, for example phenyl or naphthyl groups. Any aryl group as defined herein may be substituted with one or more substituents, for example F, Cl, Br, I, OH, NH_2, SH, N_3, NO_2, alkyl groups such as methyl or ethyl, heteroalkyl groups such as methoxy, methylamino, dimethylamino or cyanide.

The term heteroaryl refers to an aryl group as defined herein where one, two or more carbon atoms are replaced by an oxygen, nitrogen, boron, phosphorous or sulphur atom, for example 4-pyridyl, 2-imidazolyl, 3-pyrazolyl, quinolinyl, isoquinolinyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, indolyl, indazolyl, tetrazolyl, pyrazinyl, pyridinyl, pyrimidinyl and pyridazinyl groups.

The terms arylalkyl, alkylaryl and heteroarylalkyl refer to groups that comprise both aryl or, respectively, heteroaryl as well as alkyl and/or heteroalkyl and/or cycloalkyl and/or heterocycloalkyl groups.

At least two components of the inventive compounds can have the same or different pharmaceutical and/or therapeutical effects. Accordingly they can prevent, alleviate or cure the same or different diseases.

According to one embodiment of the present invention all components have different pharmaceutical and/or therapeutical effects.

According to another embodiment of the present invention all components have the same pharmaceutical and/or therapeutic effect. This embodiment is especially preferred, since such compounds can have a multiple effect on the same microorganism thereby circumventing a possible resistance mechanism.

The pharmaceutical or therapeutic effect is not especially restricted; the advantage of providing at least two pharmaceutically active components applies to all known diseases. According to one preferred embodiment the compounds

according to the present invention contain at least one or two pharmaceutically active components which have antibiotic activity. It is especially preferred that all pharmaceutically active components have antibiotic activities.

The present invention also relates to pharmaceutically acceptable salts, or solvates and hydrates, respectively, and to compositions and formulations of such compounds. The present invention describes procedures to produce pharmaceutically useful agents, which contain these compounds, as well as the use of these compounds for the production of pharmaceutically useful agents.

Examples of such pharmaceutically acceptable sufficiently basic salts of the compounds of the present invention are salts of physiologically acceptable mineral acids like hydrochloric, hydrobromic, sulfuric and phosphoric acid; or salts of organic acids like methanesulfonic, p-toluenesulfonic, lactic, acetic, trifluoroacetic, citric, succinic, fumaric, maleinic and salicylic acid. Further, examples of such pharmacologically acceptable sufficiently acidic salts of the compounds of the present invention may form alkali or earth alkaline metal salts, for example sodium, potassium, lithium, calcium or magnesium salts; ammonium salts; or organic base salts, for example methylamine, dimethylamine, trimethylamine, triethylamine, ethylenediamine, ethanolamine, choline hydroxide, N-methyl-D-aminomethane (meglumin), piperidine, morpholine, tris-(2-hydroxyethyl)amine, lysine or arginine salts. Compounds according to the present invention may be solvated, especially hydrated. The hydratisation can occur during the process of production or as a consequence of the hygroscopic nature of the initially water free compounds. The compounds can contain asymmetric C-atoms and may be present either as achiral

compounds, mixtures of diastereomers, mixtures of enantiomers or as optically pure compounds.

The present invention also relates to pro-drugs which are composed of a compound according to the present invention and at least one pharmacologically acceptable protective group which will be cleaved off under physiological conditions, such as an alkoxy-, aralkyloxy-, acyl- or acyloxy group as defined herein, e.g. ethoxy, benzyloxy, acetyl, acetyloxy, alkylcarboxyoxymethyl or 2-(alkyloxycarbonyl)-2-alkylideneethyl.

Moreover, the present invention refers to pharmaceutical compositions, containing at least one compound according to the present invention optionally in combination with pharmaceutically acceptable carriers, adjuvants and/or diluents. Optionally the pharmaceutical components according to the present invention may also contain additional known medicaments like antibiotics.

Examples of carriers, adjuvants or diluents are: water, alcohols, aqueous saline, aqueous dextrose, polyols, glycerin, petroleum, vegetable, animal or synthetic oils, glycofurol 75, 2-hydroxypropyl-β-cyclodextrin sulphobutylether-β-cyclodextrin.

As mentioned above, therapeutically useful agents that contain compounds of the present invention, their solvates, salts and formulations are also comprised in the scope of the present invention. In general, compounds of the present invention will be administered by using the known and acceptable modes known in the art, either alone or in combination with any other therapeutic agent. Such therapeutically useful agents can be administered by one of the following routes: oral, e.g. as tablets, dragees, coated tablets, pills, semisolids, soft or

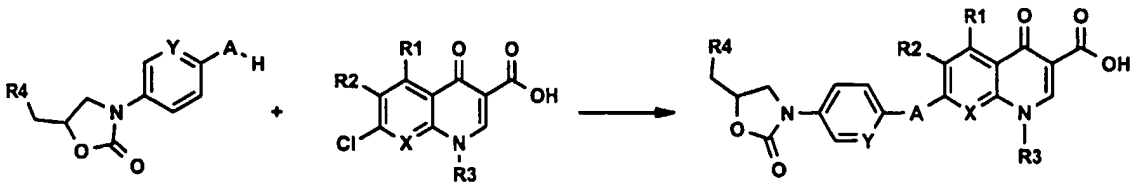
hard capsules, for example soft and hard gelatine capsules, aqueous or oily solutions, emulsions, suspensions or syrups, parenteral including intravenous, intramuscular and subcutaneous injection, e.g. as an injectable solution or suspension, rectal as suppositories, by inhalation or insufflation, e.g. as a powder formulation, as microcrystals or as a spray (e.g. liquid aerosol), transdermal, for example via an transdermal delivery system (TDS) such as a plaster containg the active ingredient or intranasal. For the production of such tablets, pills, semisolids, coated tablets, dragees and hard, e.g. gelatine, capsules the therapeutically useful product may be mixed with pharmaceutically inert, inorganic or organic excipients as are e.g. lactose, sucrose, glucose, gelatin, malt, silica gel, starch or derivatives thereof, talc, stearinic acid or their salts, dried skim milk, and the like. For the production of soft capsules one may use excipients as are e.g. vegetable, petroleum, animal or synthetic oils, wax, fat, polyols. For the production of liquid solutions, emulsions or suspensions or syrups one may use excipients as are e.g. water, alcohols, aqueous saline, aqueous dextrose, cyclodextrins, glycofurol 75, polyols, glycerin, vegetable, petroleum, animal or synthetic oils. For suppositories one may use excipients as are e.g. vegetable, petroleum, animal or synthetic oils, wax, fat and polyols. For aerosol formulations one may use compressed gases suitable for this purpose, as are e.g. oxygen, nitrogen and carbon dioxide. The pharmaceutically useful agents may also contain additives for conservation, stabilisation, e.g. UV stabilizers, emulsifiers, sweetener, aromatisers, salts to change the osmotic pressure, buffers, coating additives and antioxidants.

A daily dosage per patient of about 1 mg to about 4000 mg especially about 100 mg to 2 g is usual with those of ordinary

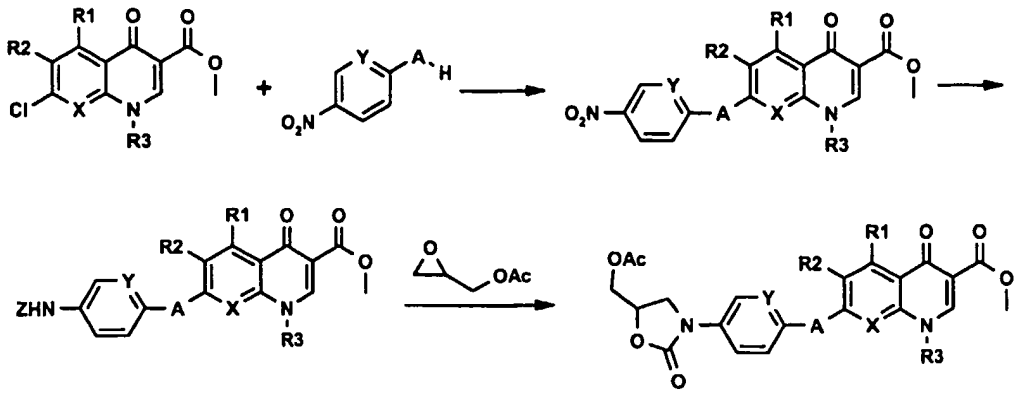
skill in the art appreciating that the dosage will depend also upon the age, conditions of the mammals, and the kind of diseases being treated or prevented. The daily dosage can be administrated in a single dose or can be divided over several doses. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg and 2000 mg can be contemplated.

The compounds, pro-drugs or pharmaceutical compositions of the present invention can e.g. be used for the treatment or prevention of viral, fungal or bacterial infections.

The compounds of Formula (I) can be obtained by reacting an oxazolidinone bearing a group A as defined above, that contains an amine with a 7-chloro quinolone derivative. To facilitate the reaction the quinolone reactant may be activated prior to its use by forming a complex with a Lewis acid like BF_3-etherate or any boron containing complex like boron acetate. The reaction is performed in a polar solvent like acetonitrile, 1-methyl-2-pyrrolidone, water, DMSO in presence of an organic base like triethylamine, N,N'dimethyl-p-toluidine, DBU, DABCO between 20 and 200°C preferably between 80 and 130°C.



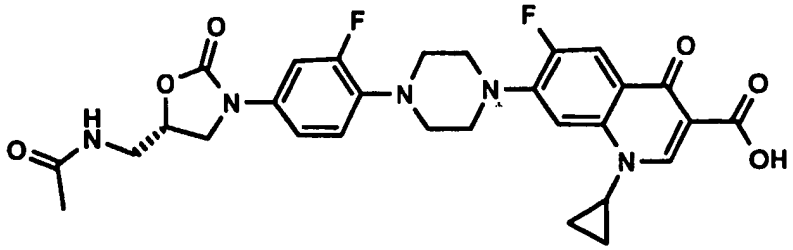
Alternatively, the product can be prepared from the corresponding 7-chloro-quinolone by substitution with a 4-nitrophenyl derivative bearing a group containing an amine and subsequent construction of the oxazolidinone through reduction of the nitro group, reaction with benzyl chloroformate, deprotonation with n-BuLi and reaction with a glycitol ester.



In the following the invention is described in more detail with reference to examples. These examples are intended for illustration only and are not to be construed as any limitation.

Examples

EXAMPLE 1: 7-(4-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:

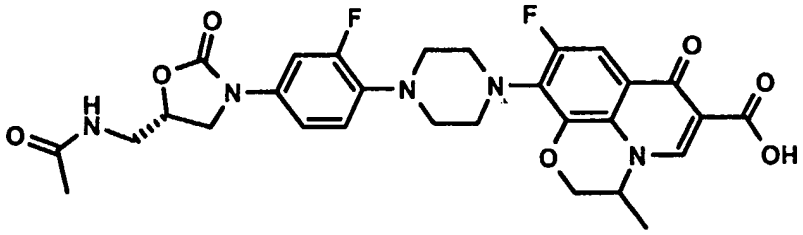


A mixture of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylate boron diacetate (described in WO8807998; 103 mg, 0.25 mmol), N-[3-(3-fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidinon-5-ylmethyl] acetamide (described in J. Med Chem 1996, 39, 673-679 and US5547950; 100mg, 0.3 mmol) and N,N'dimethyl-p-toluidine (0.054 ml, 0.375 mmol) were stirred at 120°C in 0.5 ml of 1-methyl-2-pyrrolidone for 12 hours. The reaction mixture was poured into water and the resulting

crystals were collected by filtration and purified by chromatography over silicagel. The interesting fractions were pooled affording 38 mg (26%) of beige material.

$C_{29}H_{29}F_2N_5O_6$ (581.5812)
mp 315-320°C (dec)
MS: 582.4 (M+H); 580.4 (M-H).

EXAMPLE 2: 9-(4-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:

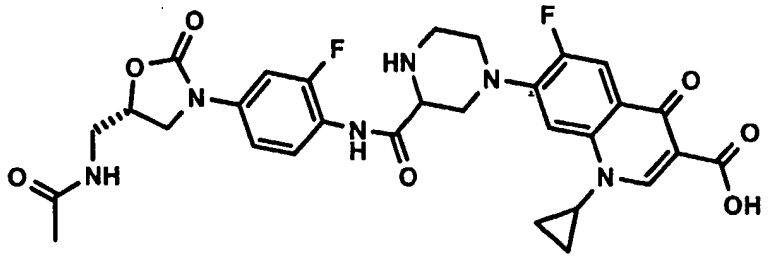


A suspension of 9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido-[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (commercially available from Aldrich (47267-0) and described in Chem. Pharm. Bull. 1987, 35, 1896-1902, 84 mg; 0.3 mmol), N-[3-(3-fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidinon-5-ylmethyl] acetamide (described in J. Med Chem 1996, 39, 673-9 and US5547950; 121mg, 0.36 mmol) and DABCO (43.7 mg, 0.39 mmol) in acetonitrile/water (7 ml, 2:1) was refluxed for 12 days. The acetonitrile was removed under reduced pressure and the residue was poured into water. The crystals were collected by filtration and further stirred in methanol (5 ml). The resulting crystals were recrystallised from DMF/ water (4:1) affording 95 mg of beige material (53%).

$C_{29}H_{29}F_2N_5O_7$ (597.5806)
mp 258°C (dec)

MS: 596.8 (M-H); 598.5 (M+H)

EXAMPLE 3: 7-((3R,S)-3-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylcarbamoyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.



2([(5S)-5-(acetylaminomethyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylcarbamoyl)-piperazine-1,4-dicarboxylic acid di-*tert*-butyl ester

0.210 ml of phosphoroxychloride was added at -15°C to a solution of 0.4 g N[(5S)-3-(4-amino-3-fluoro-phenyl)-2-oxo-oxazolidin-5-ylmethyl]acetamide (1.5 mmol) and 0.545 g piperazine-1,2,4-tricarboxylic acid 1-4-di-*tert*-butyl ester (1.65 mmol) in 10 ml pyridine. The reaction was monitored by TLC. The reaction mixture was poured on ice, diluted with dichloromethane, the org. layer washed with water and brine, dried over Mg sulfate, filtered and evaporated. The residue was purified by chromatography, using a dichloromethane/methanol 95/5 as eluent leaving a colorless foam.

Yield: 0.390 g. 45%, C27H38FN5O8 (579.63), MS: 580.5 $(M+H)^+$, 578.8 $(M-H)^-$ Method ESI^+, ESI^-

(2R,S)-2([(5S)-5-(Acetylaminomethyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylcarbamoyl)-piperazine

A solution of 0.376 g 2([(5S)-5-(acetylaminomethyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylcarbamoyl)-piperazine-1,4-dicarboxylic acid di-*tert*-butyl ester in 10 ml of dichloromethane was diluted with 10 ml of 1.25 N HCl in methanol. The reaction was monitored by TLC. The solvents were evaporated, the residue dissolved in 10 ml water, neutralized with sodium bicarbonate, and the water layer evaporated to dryness. The residue was digested in a 1/1 dichloromethane/methanol solution, the insoluble salts filtered, and the filtrate evaporated. The residue was digested in ethyl acetate and the solid filtered.
Yield: 0.250 g, quant. C17H22FN5O4 (379.39), MS: 380.5 $(M+H)^+$, method: ESI^+

7-((3R,S)-3-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylcarbamoyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.
A mixture of 175 mg 2([5-(acetylaminomethyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylcarbamoyl)-piperazine (0.46 mmol), 188 mg 7-chloro- 6-fluoro-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylatoboron diacetate and 154 mg of 1,4-diazabicyclo[2.2.2]octane (1.38 mmol) in 2 ml of N-methyl pyrrolidone was stirred at 100 °C under inert gas. The reaction was monitored by TLC. The mixture was poured in ether, the solid filtered and dried. The solid was purified by chromatography, using a dichloromethane/methanol 9/1 mixture with 1% acetic acid. The fractions with a rf of 0.1 were collected and evaporated.
Yield: 0.043 g, 18%. C30H30F2N6O7 (624.61), MS: 625.5 $(M+H)^+$, 623.8 $(M-H)^-$

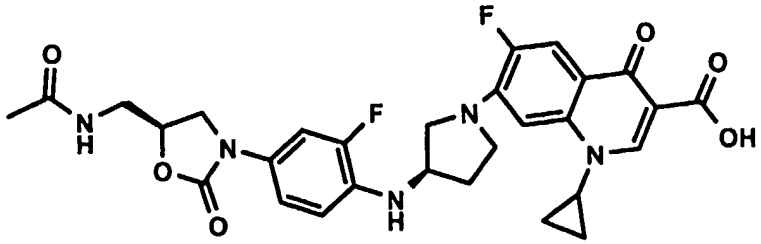
Known building blocks:

- piperazine-1,2,4-tricarboxylic acid 1-4-di-*tert*-butyl ester: CAS 181955-79-3; Com. Source : Chem. Pacific Product List N° 33681,
- 7-chloro-6-fluoro-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylatoboron diacetate:

Ger. Offen. (1996), DE 4428985.

- (S)-N[3-(4-amino-3-fluoro-phenyl)-2-oxo-oxazolidin-5-ylmethyl]acetamide: Genin, Michael et al. Journal of Medicinal Chemistry (2000), 43(5), 953-970

EXAMPLE 4: 7-[(3R)-3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-pyrrolidin-1-yl]-1cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-1-carboxylic acid.



(3R)-3-(2-Fluoro-4-nitro-phenylamino)-pyrrolidine-1-carboxylic acid allyl ester

A solution of 5.01 g of 3,4-difluoro nitrobenzene , 5.1 g (3R)-1-allyloxycarbonyl-3-amino pyrrolidine (30 mmol) and 6,27 ml of triethylamine (31.5 mmol) in 100 ml of ethyl acetate was stirred at reflux. The reaction was monitored by HPLC. The reaction was diluted with ethyl acetate, washed with water and brine, the org. layer dried over Mg sulfate, filtered and evaporated. The residue crystallized from an ether/hexane mixture.

Yield: 5.76 g, 59 %. MW: 309.29 C14H16FN3O4

1H-NMR(δ ppm, 400 MHz, D6-DMSO):1.09-2.24(m,2H, N-CH2-CH2-CH); 3.29-3.72(m, 4H,CH2- N-CH2); 4.21-4.28(m,1H, N-CH);4.52,(d,2H, O-CH2);5.15-5.32,(m,2H, CH=CH2);5.87-5.99,(m,1H, CH=CH2); 6.94,(t, 1H, Ph-CH);7.19,(d,1H, NH); 7.9-7.99,(m,2H, Ph-CH);

(3R)-3-(2-Fluoro-4-nitro-phenylamino)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

To a solution of 5.76 g (3R)-3-(2-fluoro-4-nitro-phenylamino)-pyrrolidine-1-carboxylic acid allyl ester (18.6 mmol) in 60 ml THF were added 130 mg of $PdCl_2\{P(Ph)_2\}$(0.186 mmol) ,12.12 ml acetic acid (37.2 mmol) , and 49.87 ml tributyl tinnhydride (37.2 mmol). The reaction was stirred at rt for 1 hr. and monitored by TLC. A pale yellow solid precipitated. The suspension was diluted with 100ml ether, the solid was filtered, washed with ether and hexane and dried. The solid was suspended in 10 ml THF, 4.87g BOC anhydride (, 30 mmol) was added and the reaction stirred at rt. for 3 h and monitored by TLC. The reaction was diluted with ethyl acetate, the org layer washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated. The residue was crystallized from an ether/hexane mixture.

Yield: 4.15 g, 68 %.MW: 325.34 (C15H20FN3O4)

1H-NMR (400 MHz,D6-DMSO; δ ppm):1.25,(s,9H,t-but);1.75-2.07(m,2H, N-CH2-CH2-CH); 3.07-3.5(m, 4H,CH2- N-CH2); 4.05-4.1(m,1H, N-CH); 6.77-6.83,(t, 1H, Ph-CH);7.01,(d,1H, NH); 7.77-7.858,(m,2H, Ph-CH);

(3R)-3-[Benzyloxycarbonyl-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-amino]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

To a solution of 4 g of (3R)-3-(2-fluoro-4-nitro-phenyl-amino)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (12.29 mmol) in 100 ml ethyl acetate and 50 ml methanol were added 1g of Pd/C 10%. The suspension was stirred under hydrogen. The reaction was

monitored by TLC. The catalyst was filtered, the filtrate evaporated to dryness, and the residue was dissolved in 100 ml of acetone. 25 ml of a saturated solution of sodium bicarbonate was added, than a 0°C 3.63 ml of benzyl chloroformate (25.8 mmol). The reaction was stirred over night at rt and monitored by TLC. The acetone was evaporated, the water layer extracted twice with ethyl acetate, the org layer washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated to dryness. The residue was purified by chromatography, using a 1/1 ethyl acetate/hexane mixture as eluent.
Yield: 6.03 g, 99 %. MW: 563.63, C31H34FN3O6, MS: 562.4 $(M-H)^-$, Method ESI^-.

(3R)-3-{Benzyloxycarbonyl-[2-fluoro-4-{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenyl]-amino}-pyrrolidine-1-carboxylic acid *tert*-butyl ester
To a solution of 6.02g (3R)-3-[benzyloxycarbonyl-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-amino]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (10.8 mmol) in 40 ml THF at -78°C was added dropwise 7.62 ml of a 1.6 M N-butyl-lithium solution in N-hexane (12.2 mmol). The mixture was stirred at -78°C for 10 min, than allowed to reach 0°C. 2.11 g of R(-)-glycidyl butyrate (14.6 mmol) was added. The reaction was allowed to reach 20°C and was monitored by TLC. The reaction was diluted with ethyl acetate, washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated. The residue was crystallized from an ethyl acetate/hexane mixture.
Yield: 3.36 g, 60 %. MW:529.47,(C27H32FN3O7) MS: 530.3 $(M+H)^+$, Method ESI^-.

(3R)-3-{[4-{(5R)-5-Azidomethyl-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl]-benzyloxycarbonyl-amino}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

To a solution 3.36 g of (3R)-3-{benzyloxycarbonyl-[2-fluoro-4-{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenyl]-amino}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (10.8 mmol) and 2.05 ml of triethylamine (10.8 mmol) in 40 ml of dichloromethane, was added at 0°C 0.805 ml of methanesulfonyl chloride (10.8 mmol). The reaction was stirred at rt. and monitored by TLC. The reaction was diluted with water and washed with water and brine. The org. layer was dried over Mg sulfate, filtered and the filtrate evaporated .The solid residue was dissolved in 10 ml of DMF and 1.38g sodium azide (10.8 mmol) was added and the mixture stirred under inert gas at 80°C for 20 hrs. The DMF was evaporated, the residue dissolved in ethyl acetate, washed with water and brine, dried over Mg sulfate, filtered and evaporated.

Yield: 4.07 g, 99 %. MW:554.58, (C27H31FN6O6) MS: 555.5 $(M+H)^+$, Method ESI^+.

(3R)3-{4-[(5S)-5-(Acetylaminomethyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

To a stirred solution of 4.2 g of (3R)-3-{[4-{(5R)-5-azidomethyl-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl]-benzyl-oxycarbonyl-amino}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (7.3 mmol) in 50 ml ethyl acetate were added 400 mg of Pd/C 10% and the mixture was stirred under hydrogen over night. The reaction was controlled by TLC. The Pd/C was filtered , the filtrate evaporated to dryness. The residue was dissolved in 5 ml acetic acid and 2 ml acetic anhydride was added. The reaction was stirred at rt for 2hrs and monitored by TLC. The solvents were evaporated, the residue dissolved in ethyl

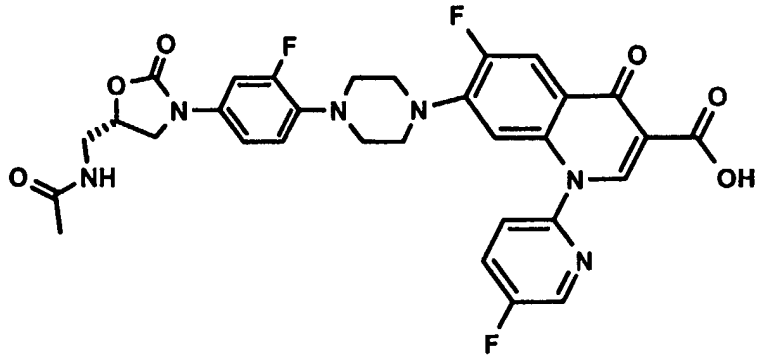
acetate, washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated to dryness.
Yield: 3.1 g, quantitative. MW : 436.48,(C21H29FN4O5) MS: 437.5 $(M+H)^+$, Method ESI^+.

N-{(5S)-3-[3-Fluoro-4-{(3R)-pyrrolidin-3-ylamino}-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide.
A solution of 0.93 ml triethylsilane (7.3 mmol) (3R)3-{4-[(5S)-5-(acetylaminomethyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-pyrrolidine-1-carboxylic acid tert-butyl ester (, 7.3 mmol) in 40 ml of a CH2Cl2/TFA 1/1 mixture was stirred at rt and monitored by TLC. The solvents were evaporated, the residue dissolved in water and neutralized with a saturated sodium bicarbonate solution. The water was evaporated, the residue digested in a 1:1 CH2Cl2/MeOH solution, the solution treated with 500 mg of Fuller's earth, filtered and the filtrate evaporated.
Yield: 2.1 g, 85%. MW:336.36, (C16H21FN4O3) MS: 337.6 $(M+H)^+$, Method ESI^+.

7-[(3R)-3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-pyrrolidin-1-yl]-1cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-1-carboxylic acid.
A solution of 204 mg 7-chloro- 6-fluoro-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylatoboron diacetate (0.5 mmol), 252 mg N-{(5S)-3-[3-fluoro-4-{(3R)-pyrrolidin-3-ylamino}-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (0.75 mmol) and 112 mg DABCO (MW: 112.0, 1 mmol) in 5 ml DMSO was stirred for 50h. The DMSO was evaporated. The residue was suspended in 10 ml ethanol with 100 µl triethylamine and stirred at room temperature for 20 hrs. The mixture was diluted with 20 ml water. The mixture was filtered and the solid collected. The solid was crystallized in a methanol /ethanol/ dichloromethane mixture

Yield: 16 mg, 3.6%.MW:582.4, (C29H29F2N5O6) MS: 582.4 $(M+H)^+$, Method ESI^+.

EXAMPLE 5: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6-fluoro-1-(5-fluoro-pyridin-2-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



7-Chloro-6-fluoro-1-(5-fluoro-pyridin-2-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester.

A solution of 0.747g of 2-(2,4-dichloro-5-fluoro-benzoyl)-3-ethoxy-acrylic acid ethyl ester (2.23 mmol) and 0.250 g of 2-amino-5-fluoropyridine (2.23 mmol) in 5 ml ethanol was stirred at reflux for 25 hrs. The reaction was monitored by TLC. The ethanol was evaporated and the last traces of ethanol were distilled from an azeotrope with a mixture of 10ml heptane and 10 ml ethyl acetate. The yellow oil was dissolved in 10 ml of THF, reacted with 120 mg of a 50% NaH suspension in oil and stirred at reflux over night. The solvent was evaporated, the residue dissolved in dichloromethane/methanol 9:1, washed with water and brine, dried over Mg sulfate, filtered and evaporated. The residue was digested in ethyl acetate, and the solid filtered.

Yield: 583 mg, 72%. MW:364.73, (C17H11ClF2N2O3) MS: 365.4 $(M+H)^+$, Method ESI^+.

7-chloro-6-fluoro-1-(5-fluoro-pyridin-2-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

A suspension of 0.5 g 7-chloro-6-fluoro-1-(5-fluoro-pyridin-2-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (1.37 mmol) in a mixture of 1.5 ml acetic acid and 1.5 ml 25% HCl was stirred at 90°C over night. The reaction was monitored by HPLC. The suspension was poured into 50 ml water, the colorless crystals filtered and dried.

Yield: 461 mg, quant. MW:336.68, (C15H7ClF2N2O3) MS: 337.5 $(M+H)^+$, Method ESI^+.

7-chloro-6-fluoro-1-(5-fluoro-pyridin-2-yl)-4-oxo-1,4-dihydro-quinoline-3- carboxylatoboron diacetate.

To a stirred suspension of 380 mg 7-chloro-6-fluoro-1-(5-fluoro-pyridin-2-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (1.12 mmol) in 4 ml dichloromethane were added at 0°C 0.31 ml triethylamine (d=0.726, 2.25 mmol) and 0.12 ml (d=1.1050, 1.68 mmol) acetyl chloride. The reaction mixture was allowed to warm up to RT, diluted with dichloromethane and washed twice with ice cold water and brine. The organic layer was dried over sodium sulfate, filtered and evaporated. The residue was crystallized from a dichloromethane/ hexane mixture. 332 mg of the colorless crystals were suspended in 0.63 ml of acetic anhydride (MW: 102.9, d=1.08, 6.6 mmol), 78 mg anhydrous boric acid (MW: 61.83, 1.26 mmol) and 1 mg zinc chloride (MW: 136.28,0. 7mmol) were added. The mixture was stirred at 80°C for two hours. The reaction was poured on 10 g ice in 20 ml water and stirred. The colorless crystals were filtered, digested twice in 100 ml ethanol, filtered, washed with ether and hexane, and dried at RT under vacuum.

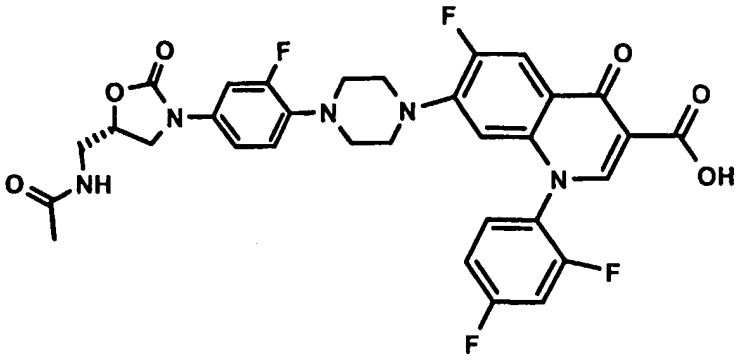
Yield: 226 mg, 43 %. MW:464.57, ($C_{19}H_{12}BClF_2N_2O_7$)
1H-NMR (δ ppm; DMSO-D_6): 1.96 (s, 6 H, acetate); 8.15 (d, 1H, pyridin), 8.25 (m, 2H, pyridin), 8.53 (d, 1H, quinoline); 8.87 (d, 1H, quinoline); 9.71 (s, 1H, allyl).

7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6-fluoro-1-(5-fluoro-pyridin-2-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.
212 mg of 7-chloro-6-fluoro-1-(5-fluoro-pyridin-2-yl)-4-oxo-1,4-dihydro-quinoline-3- carboxylatoboron diacetate (, 0.45 mmol), 306 mg N-{[(5S)-3-[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl}-acetamide (0.9 mmol) and 2 ml DMSO were irradiated in a microwave oven for 7 periods of 2.30 min at 250 W in a closed reaction vessel under inert gas. The reaction was monitored by HPLC.
The DMSO was evaporated and the crude product was digested in 10 ml water and filtered. The residue was purified by chromatography using a CH_2Cl_2/MeOH 5% mixture.
Yield: 5 mg, 2 %. MW:636.59, ($C_{31}H_{27}F_3N_6O_6$) MS: 637.2 $(M+H)^+$, Method ESI^+.

Known building blocks:

- 2-amino-5-fluoropyridine: 21717-96-4, aldrich 51868-9
- 2-(2,4-Dichloro-5-fluoro-benzoyl)-3-ethoxy-acrylic acid ethyl ester: 86483-52-5,WO0217916 A1

EXAMPLE 6: 7-(4-{(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



7-Chloro-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

A solution of 2 g 2-(2,4-dichloro-5-fluoro-benzoyl)-3-ethoxy-acrylic acid ethyl ester (5.97 mmol) and 0.6 ml of 2,4-difluoroaniline (5.97 mmol) in 15 ml of ethanol was stirred at reflux for 25 hrs. The reaction was monitored by TLC. The ethanol was evaporated and the residual ethanol was distilled from an azeotrope with 20 ml heptane and 20 ml ethyl acetate. The yellow oil was dissolved in 20 ml of THF, reacted with 315 mg of a 50 % NaH suspension in oil (6.56 mmol) and stirred at reflux for 20 hrs. The solution was diluted with ethyl acetate, washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated.

Yield: 2,0 g, 90 %. MW:381.74, ($C_{18}H_{11}ClF_3NO_3$) MS: 382.3 $(M+H)^+$, Method ESI^+.

7-Chloro-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

A mixture of 2,0 g of 7-chloro-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (5.23 mmol) in 16 ml acetic acid and 16 ml HCl 37% was stirred 25 hrs at 90°C, and evaporated.

Yield: 1,71 g, quantitative. MW:353.68,($C_{16}H_7ClF_3NO_3$) MS: 354.3 $(M+H)^+$, Method ESI^+.

7-Chloro-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylatoboron diacetate

To a stirred suspension of 1,71g 7-chloro-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (4.84 mmol) in 4 ml of dichloromethane were successively added at 0°C 1,35 ml triethylamine (MW:101.19, 9.68 mmol) and 0,517 ml acetyl chloride (MW: 78.50, d=1.1050,7 26 mmol). The reaction mixture was allowed to warm up to RT, diluted with dichloromethane and washed twice with ice cold water and brine. The org. layer was dried with sodium sulfate, filtered and evaporated. The residue was crystallized from a dichloromethane/ hexane mixture.

1,91 g of the colorless crystals were suspended in 3,21ml of acetic anhydride (33.88 mmol), 400 mg anhydrous boric acid (6.47mmol) and 5 mg zinc chloride (0.04 mmol) were added. The mixture was stirred at 80°C for two hours. The reaction was poured on 10 g ice in 20 ml water and stirred. The colorless crystals were filtered, digested twice in 100 ml ethanol, filtered, washed with ether and hexane, and dried.

Yield: 1,7 g, 74 %. MW:481.58, ($C_{20}H_{12}BClF_3NO_7$) MS: 482.4 $(M+H)^+$, Method ESI^+.

7-(4-{(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

A suspension of 240mg of 7-chloro-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylatoboron diacetate (0.5 mmol) and 336 mg N-({(5S)-3-[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl}-methyl)-acetamide (1 mmol) in 2 ml DMSO were irradiated in a microwave oven for three 2,30 min periods at 250W in a close reaction vessel under inert gas. The reaction was monitored by HPLC. The DMSO was evaporated and the residue was digested in acetonitrile /water. The solid

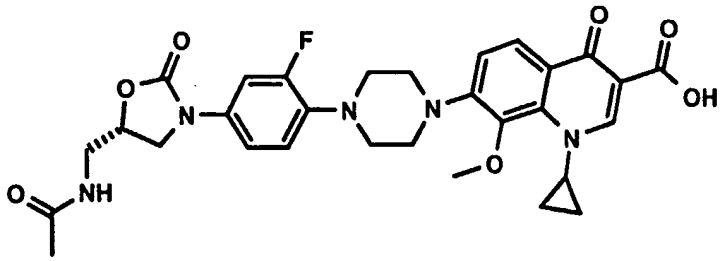
was filtered off and the filtrate evaporated and purified by chromatography.

Yield: 11 mg, 4%.MW:653.60, (C32H27F4N5O6) MS: 652.5 $(M-H)^-$, Method ESI^-.

Known building blocks

- 2,4-difluoroaniline: 367-25-9, Aldrich D10-140-0
- 2-(2,4-Dichloro-5-fluoro-benzoyl)-3-ethoxy-acrylic acid ethyl ester: 86483-52-5,WO0217916 A1 20020307

EXAMPLE 7: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclo-propyl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



1-Cyclopropyl-7-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylatoboron diacetate

To a stirred suspension of 1,12 g of 1-cyclopropyl-7-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (4 mmol) in 20 ml of dichloromethane were successively added at 0°C 1,2 ml triethylamine (8 mmol) and 0.454 ml acetyl chloride (MW: 78.50). The reaction mixture was allowed to warm up to RT, diluted with dichloromethane and washed twice with ice cold water and brine. The organic layer was dried with sodium sulfate, filtered and evaporated. The crystals were suspended in 3 ml of acetic anhydride (MW: 102.9,28 mmol) and 354 mg anhydrous boric acid (MW: 61.83, 5.6mmol) and 10 mg zinc

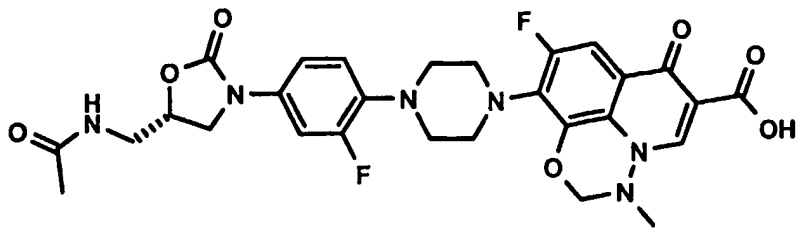
chloride (MW: 136.28,0.07mmol) were added. The mixture was stirred at 80°C for two hours. The reaction was poured on 10g ice in 20 ml water and stirred. The colorless crystals were filtered.
Yield: 600 mg, 46%. MW:405.14, (C18H17BFNO8) MS: 406.5, $(M+H)^+$, Method ESI^+.

7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
A solution of 100 mg 1-cyclopropyl-7-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylatoboron diacetate (0.24 mmol), 166mg of N-[[3-[(5S)-3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.49 mmol) and 59 µl ethyldiisopropylamine (0.336 mmol) in 1 ml DMSO was irradiated in a microwave oven for 10 min at 150°C. The reaction was monitored by HPLC. The DMSO was evaporated and the residue was purified by chromatography using a CH_2Cl_2/MeOH 5 % mixture.
Yield: 14 mg, 10 %.MW:593.62, (C30H32FN5O7). MS: 594.6 $(M+H)^+$, Method ESI^+.

Known building blocks

- 1-Cyclopropyl-7-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:221221-16-5, US6329391
- N-[[3-[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide:154590-43-9,US 5547950

EXAMPLE 8: 9-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3,3a-diaza-phenalene-5-carboxylic acid:



9-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3,3a-diaza-phenalene-5-carboxylic acid ethyl ester.

A solution of 100 mg 8,9-difluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3,3a-diaza-phenalene-5-carboxylic acid ethyl ester (0.32 mmol) and 216 mg of N-[{(5S)-3[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl}-methyl]-acetamide (0.64 mmol) were dissolved in a mixture of 1 ml pyridine and 1 ml DMSO. The reaction was monitored by TLC. The DMSO was evaporated, the residue digested in water and the solid collected. The solid was purified by chromatography, using a 9/1 dichloromethane / methanol mixture as eluent.

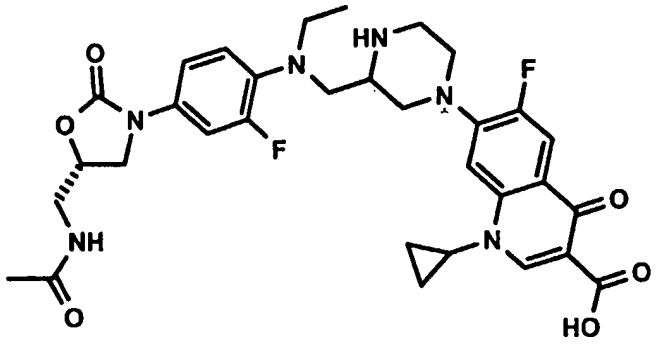
Yield: 44 mg 22%. MW:626.62, (C30H32F2N6O7) MS: 627.7 $(M+H)^+$, Method ESI^+

9-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3,3a-diaza-phenalene-5-carboxylic acid.

44 mg of 9-(4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3,3a-diaza-phenalene-5-carboxylic acid ethyl ester (0.32 mmol) were heated at 80°C in 2 ml of a 1/1 conc. HCl and acetic acid mixture. The reaction was monitored by HPLC. The HCl/AcOH mixture was evaporated, the residue dissolved in a methanol/dichloromethane 1/1 mixture, treated with triethylamine and evaporated. The deacetylated residue was dissolved in a 1/1 mixture acetic acid and acetic anhydride, and

the reaction monitored by HPLC. The solvents were evaporated and the residue was purified by preparative HPLC.
Yield: 9.1 mg 21%. MW:598.56, ($C_{28}H_{28}F_2N_6O_7$) MS: 599.2 $(M+H)^+$, 597.7 $(M-H)^-$, Method ESI^+, ESI^-

EXAMPLE 9: 7-{(3RS)-3-[({4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-ethyl-amino)methyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.



(1,4-Dibenzyl-piperazin-2-ylmethylen)-ethyl-amine
To a solution of 0.5g (1,4-bis(phenylmethyl)-2-piperazin-carboxaldehyd in 5ml of dichloromethane was added 0.54 ml ethylamine and 0.5 g molecular sieves. The reaction mixture was stirred for 30 min at rt then filtered. The filtrate was evaporated to dryness.
Yield: 385 mg, 71%. MW: 321.46, ($C_{21}H_{27}N_3$)
1H-NMR(400 MHz,D6-DMSO; δ ppm):1.07(t,3H, N-CH2-CH3); 2.07-2.22(m, 3H, N-CH2); 2.63-2.73(m,3H, N-CH2)2.92(m,1H, pip.H2);3.25-3.74(AB,2H, CH2-Ph); 3.41-3.53(AB,2H, CH2-Ph);7.22-7.35(m,10 H,Ph);7.6(d,1H, methylene).

[(2R,S)-(1,4-Dibenzyl-piperazin-2-ylmethyl)]-ethyl-amine
0.92 g of sodium borohydride were added to a stirred solution of 5.24g of [(2R,S)-1,4-dibenzyl-piperazin-2-ylmethylen]-ethylamine

in 50ml dry THF and 3 ml ethanol under inert gas. The reaction mixture was stirred at rt for 6 hrs. Second and third portions of 0.92 g of sodium borohydride were added after 8 and 12 hrs respectively. The reaction was quenched with 20 ml of HCl 0.1M. The reaction mixture was diluted with ethyl acetate and the organic layer was washed with water and brine, dried over MgSO4, filtered and the filtrate evaporated to give 5.5 g of an oil. The oil was purified by chromatography over SiO2 with a 1/1 hexane/acetone mixture with 1% triethylamine

Yield: 2.1g , 40%. MW:323.48, (C21H29N3)

^{1}H-NMR(400 MHz,D_6-DMSO; δ ppm):0.91(t,3H, N-CH2-CH3); 2.07-2.23(m, 3H, N-CH2); 2.38-2.52(m,4H, N-CH2); 2.60-2.70(m, 4H, N-CH, N-CH2);3.21-3.26 and 3.97-4.01(AB,2H, CH2-Ph); 3.36-3.47(AB,2H, CH2-Ph); 7.18-7.33 (m,10H, Ph-H)

[(2R,S)-1,4-Dibenzyl-piperazin-2-ylmethyl]-ethyl-(2-fluoro-4-nitro-phenyl)-amine

A mixture of 1.057 g of 3,4-difluoro-nitrobenzene (6.34 mmol), 2.05 g [(2R,S)1,4-dibenzyl-piperazin-2-ylmethyl]-ethylamine (6.34 mmol) and 1.4 ml triethylamine (9.9 mmol) in 10 ml of ethyl acetate was stirred at 60°C . The reaction was monitored by TLC .The reaction was diluted with ethyl acetate, washed with water and brine, dried over Mg sulfate and filtered. The filtrate was evaporated and the residue was purified by chromatography using an ethyl acetate/hexane 3/7 mixture as eluent. The interesting fractions were collected and evaporated to leave a yellow sticky oil.

Yield: 2.58 g, 88%. MW:462.57, (C27H31FN4O2) MS: 463.3 $(M+H)^+$, Method ESI^+.

(4-[{(2R,S)-1,4-Dibenzyl-piperazin-2-ylmethyl}-ethyl-amino]-3-fluoro-phenyl)-carbamic acid benzyl ester

To a solution of 2.58g((2R,S)-1,4-dibenzyl-piperazin-2-ylmethyl)-ethyl-(2-fluoro-4-nitro-phenyl)-amine in 100 ml methanol was sequentially added 50 ml of a saturated solution of ammonium chloride in water and 0.5 g zinc dust. The mixture was vigorously stirred and monitored by TLC. The solid was filtered, the filtrate concentrated and the solid deep red material filtered from the aqueous layer. The solid was dissolved in ethyl acetate, washed twice with water and brine, dried over Mg sulfate, filtered and evaporated.

The deep red oily residue was dissolved in 100 ml acetone. 50 ml of saturated sodium bicarbonate solution was added. Under vigorous stirring, 1.17 ml of benzylchloroformate were added at 0°C. The reaction was stirred at rt over night, the acetone evaporated and the water layer extracted twice with ethyl acetate. The org. layer was washed with water and brine, dried over Mg SO_4, filtered and the filtrate evaporated. The residue was purified by chromatography, using a 95/5 dichloromethane/methanol mixture as eluent.

Yield: 3.1 g, quantitative. MW:566.72, (C35H39FN4O2)

^{1}H-NMR(400 MHz,D_6-DMSO; δ ppm):0.95(t,3H, N-CH2-CH3); 2.26-2.39(m, 3H, N-CH2); 2.55-2.70(m,2H, N-CH2); 2.99-3.05(m, 2H, N-CH2); 3.18-3.25(m, 1H, N-CH2); 3.43-3.50(m,3H,-NH2); 4.04-5.25 and 4.54-5.20(AB,4H, CH2-Ph); 3.36-3.47(AB,2H, CH2-Ph); 6.96-7.07(t, 1H, Ph-H); 7.09-7.12(dd,1H,Ph-H); 7.23-7.49(m, 16H, Ph-H); 9.82(s,1H, N-H).

(5R)-3-{4-[{(2R,S)-1,4-Dibenzyl-piperazin-2-ylmethyl}-ethyl-amino]-3-fluoro-phenyl}-5-hydroxymethyl-oxazolidin-2-one

To a solution of 3.1 g (4-[{(2R,S)-1,4-dibenzyl-piperazin-2-ylmethyl}-ethyl-amino]-3-fluoro-phenyl)-carbamic acid benzyl ester (5.4 mmol) in 25 ml THF at -78°C was added dropwise 4.38 ml of a butyl-lithium solution (1.6M, 7 mmol) in N-hexane. The mixture was stirred at -78°C for 10 min, than allowed to reach -

40°C for 10 min. 1.28 g of R(-)-glycidyl butyrate (8.92 mmol) was added. The reaction was allowed to reach 20°C and was monitored by TLC. The reaction was diluted with ethyl acetate, washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated. The residue was purified by chromatography, using a 92.5/7.5 dichloromethane/methanol mixture as eluent.
Yield: 2.35 g 69%. MW:532.68, (C31H37FN4O3) MS: 533.1 $(M+H)^+$, Method ESI^+.

Methanesulfonic acid (5R)-3-{4-[{(2R,S)-1,4-Dibenzyl-piperazin-2-ylmethyl}-ethyl-amino]-3-fluoro-phenyl}-2-oxo-oxazolidin-5-ylmethyl ester
To a solution of 1.2 g of (5R)-3-{4-[{(2R,S)-1,4-dibenzyl-piperazin-2-ylmethyl}-ethyl-amino]-3-fluoro-phenyl}-5-hydroxymethyl-oxazolidin-2-one (2.25 mmol) and 0.5 ml of triethylamine (4.5 mmol) in 10 ml of dichloromethane was added at 0°C 0.272 g of methansulfonyl chloride (2.4 mmol). The reaction was stirred at 25°C and monitored by TLC. The reaction was quenched with water, the org. layer washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated. The oily residue was purified by chromatography using a 95/5 dichloromethane /methanol mixture with 0.5% triethylamine. The fractions with a rf of 0.18 were collected and evaporated.
Yield: 1.02g, 75%, MW:610.75, (C32H39FN4O5S) MS: 611.1 $(M+H)^+$, Method ESI^+.

(5R)-5-Azidomethyl-3-{4-[{(2R,S)-1,4-Dibenzyl-piperazin-2-ylmethyl}-ethyl-amino]-3-fluoro-phenyl} -oxazolidin-2-one
A suspension of 1.16 g of methanesulfonic acid-(5R)-3-{4-[{(2R,S)-1,4-dibenzyl-piperazin-2-ylmethyl}-ethyl-amino]-3-fluoro-phenyl}-2-oxo-oxazolidin-5-ylmethyl ester (1.89 mmol),

0.245mg sodium azide (MW: 65.01, 3.7 mmol) and 29 mg of sodium iodide (0.0189 mmol) in 5 ml of DMF was stirred under inert gas at 80°C. The reaction was monitored by TLC. The DMF was evaporated, the residue dissolved in ethyl acetate, washed with water and brine, dried over Mg sulfate than filtered and the filtrate evaporated. The oily residue was purified by chromatography using a 95/5 dichloromethane/ methanol mixture with 0.25% triethylamine as eluent. The fractions with a rf of 0.19 were collected and dried.
Yield: 0.89 g, 84%. MW:557.67, ($C_{31}H_{36}FN_7O_2$) MS: 558.3 $(M+H)^+$, Method ESI^+.

N-[(5S)-3-{4-[{(2R,S)-(1,4-Dibenzyl-piperazin-2-ylmethyl}-ethyl-amino]-3-fluoro-phenyl} -2-oxo-oxazolidin-5-ylmethyl]-acetamide.
A solution of 889 mg (5R)-5-azidomethyl-3-{4-[{(2R,S)-1,4-dibenzyl-piperazin-2-ylmethyl}-ethyl-amino]-3-fluoro-phenyl}-oxazolidin-2-one (1.59 mmol), 459 mg triphenylphosphine (1.75 mmol) and 286 mg water (15.94 mmol) in 20 ml of THF was stirred at 50°C for 22 hrs. The reaction was monitored by TLC. The THF was evaporated and the residue dissolved in 2 ml acetic anhydride. The reaction was monitored by TLC. The solvent was evaporated and the residue was purified by chromatography using a 95/5 dichloromethane/methanol mixture with 0.5% triethylamine as eluent leaving a sticky oil.
Yield: 0.6 g, 65%. MW:573.71, ($C_{33}H_{40}FN_5O_3$) MS: 574.2 $(M+H)^+$, Method ESI^+.

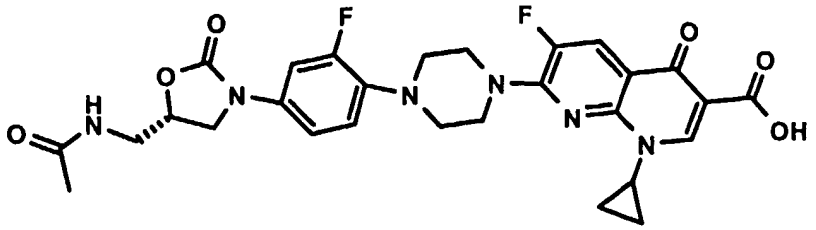
N-[(5S)-3-{4-[{(2R,S)-Piperazin-2-ylmethyl}-ethyl-amino]-3-fluoro-phenyl} -2-oxo-oxazolidin-5-ylmethyl]-acetamide.
A suspension of 0.59 g N-[(5S)-3-{4-[{(2R,S)-(1,4-dibenzyl-piperazin-2-ylmethyl}-ethyl-amino]-3-fluoro-phenyl}-2-oxo-oxazolidin-5-ylmethyl]-acetamide (1.028 mmol) and 300 mg Pd/C in 20 ml of a 1/1 ethyl acetate/methanol mixture was stirred under

H2 at room temperature. The reaction was monitored by TLC. The Pd/C was filtered and the filtrate evaporated to dryness. The glassy residue was dried.
Yield: 0.3 g, 86%. MW:393.46, (C19H28FN5O3) MS: 394.3 $(M+H)^+$, Method ESI^+.

7-{(3R,S)-3-[({4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-ethyl-amino)methyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.
A suspension of 115 mg of 7-chloro- 6-fluoro-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylatoboron diacetate (0.282 mmol), 100 mg N-[(5S)-3-{4-[{(2R,S)-piperazin-2-ylmethyl}-ethyl-amino]-3-fluoro-phenyl}-2-oxo-oxazolidin-5-ylmethyl]-acetamide and 35 mg DABCO in 1 ml DMSO was heated in a micro wave oven for 10 periods of 2.5 min. at 240W. The reaction was monitored by TLC. The DMSO was evaporated, the residue dissolved in 10ml dichloromethane and the solid collected. The solid was digested in 3 ml water, filtered and purified by prep HPLC. The fractions were concentrated by evaporation and the water freezed dried.
Yield: 13.5 mg, 7.6 %. MW:638.67, (C32H36F2N6O6) MS: 639.4 $(M+H)^+$, Method ESI^+.

Known building block:
(1,4-Bis(phenylmethyl)-2-piperazincarboxaldehyde
Lit. Naylor Alan and all. Eur. Pat.Appl (1989), EP 343900

EXAMPLE 10: 7-(4-{[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



7-(4-{[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid.

A suspension of 100 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid 0.35 mmol), 130 mg N-[{(5S)-3[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl}methyl]-acetamide (0.39 mmol) 119 mg triethylamine (MW: 101.19, 1.17 mmol) and 85 mg trimethylchlorsilan (0-78 mmol) in 2 ml DMSO was heated at 150°C under stirring in a microwave oven for 10 min. The reaction was monitored by TLC. The DMSO was evaporated, the residue digested in water, filtered and the solid purified by chromatography, using dichloromethane / methanol mixture as eluent. The fractions were collected and evaporated. The residue was crystallized from acetonitrile.

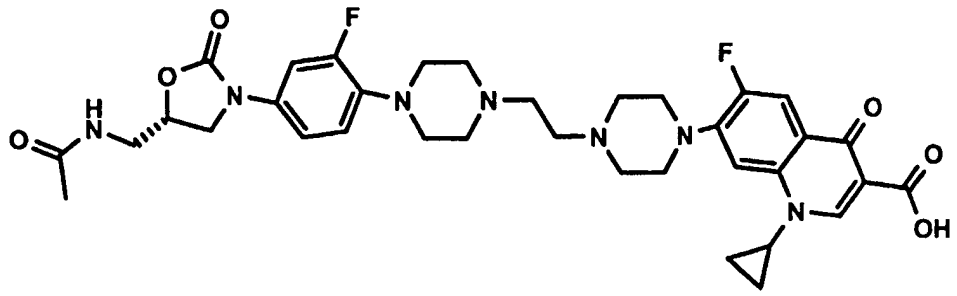
Yield: 84 mg, 42%. MW:582.57, (C28H28F2N6O6) MS: 583.3 $(M+H)^+$, 581.6 $(M+H)^-$ Method ESI^+, ESI^-

Known building blocks

- 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid
  Lit.: US 4777175; US 5281612; CAS: 100361-18-0
- N-[{(5S)-3[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl}methyl]-acetamide
  Lit. US 5547950 CAS: 154590-66-6

EXAMPLE 11: 7-{4-[2-(4-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-ethyl]-

piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



4-[2-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazine1-yl)ethyl]piperazine-1-carboxylic acid tert butyl ester

A solution of 336 mg of N-({(5S)-3-[-3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl}methyl)-acetamide (1 mmol), 308 mg of 4-[2-{2-(methylsulfonyl)-oxy}-ethyl]-1-piperazinecarboxylic acid-1,1-dimethylethyl ester (1 mmol), 32.2 mg of tetrabutylammonium iodide (0.08 mmol) and 203 mg of potassium carbonate (2.5 mmol) in 2 ml DMF was stirred at 80° for 20 h. The solvent was evaporated and the residue purified by prep HPLC.

Yield: 200 mg, 36 %. C27H41FN6O5 (Mw: 548.6) MS: $(M+H)^+$ 549.5, Method ESI^+.

N-[(5S)-3-{3-Fluoro-4-[4-(2-piperazin-1-yl-ethyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5ylmethyl]-acetamide

A solution of 200 mg of 4-[2-(4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazine-1-yl)ethyl]piperazine-1-carboxylic acid tert butyl ester (0.36 mmol) in 2 ml dichloromethane and 2 ml trifluoracetic acid was stirred for 10 min. The solvents were evaporated, the residue was digested in ether and the solid filtered. The solid was dissolved in water and neutralized with a saturated solution of

sodium bicarbonate. The water was evaporated and the product dried as a mixture with the salts.
Yield: 136 mg, 100 %. C22H33FN6O3 (Mw: 448.5) MS: 449.4 $(M+H)^+$, Method ESI^+.

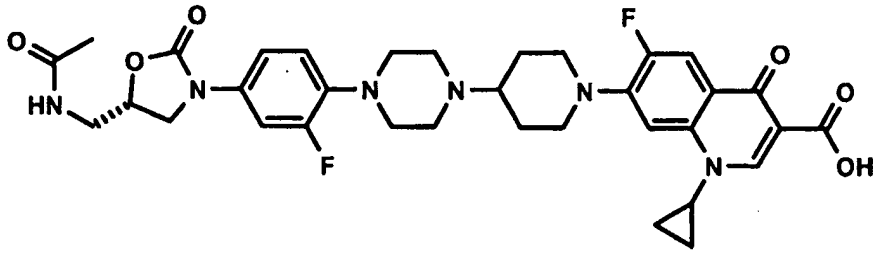
6.7-Difluoro-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylatoboron diacetate
To a suspension of 2 g of 1-cyclopropyl-6, 7 difluoro-1, 4-dihydro-4-oxo-3-quinolinecarboxylic acid (0.754 mmol) in 30ml dichloromethane was added at 0°C, 2.10 ml triethylamine (1.52mmol) and 804 µl acetyl chloride (1.1 mmol). The solution was allowed warm up to RT. The mixture was then diluted with dichloromethane and washed twice with water and brine. The organic layer was dried over MG sulfate, filtered and the filtrate evaporated. The solid was suspended in 5,08 ml of acetic anhydride (5.2 mmol), 628 mg anhydrous boric acid (MW: 61.83, 1 mmol) and 20 mg zinc chloride (0.14 mmol) were added. The mixture was stirred at 80°C for 20 hrs. The reaction was poured on 10-g ice in 20 ml water and stirred. The solid was filtered.
Yield: 1.4 g 47 %. C17H14BF2NO7 (Mw: 393.1) MS: 394.1 $(M+H)^+$, Method ESI^+.

7-{4-[2-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxalidin-3-yl]-2-fluoro-phenyl}-piperazin-1yl)-ethyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
A mixture of 163 mg of N-[(5S)-3-{3-fluoro-4-[4-(2-piperazin-1-yl-ethyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5ylmethyl]-acetamide (0.36mmol), 142,85 mg of 6.7-difluoro-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylatoboron diacetate (0.36 mmol) and 44,77 mg DABCO (0.36mmol) was irradiated in a micro wave oven for three periods of 3 min. The reaction was followed

with HPLC. DMSO was evaporated and the residue purified by preparative HPLC.
Yield: 40 mg, 16 %. C35H41F2N7O6; (Mw: 693.7) MS: 694.3$(M+H)^+$, 692.6$(M-H)^-$, Method ESI^+, Method ESI^-

Known building blocks:
1-piperazinecarboxylic acid, 4-[2-[2-[methylsulfonyl) oxy]-ethyl]-1-piperazinecarboxylic acid-1,1-dimethylethyl ester: WO 8808424
1-cyclopropyl-6, 7 difluoro-1, 4-dihydro-4-oxo-3-quinoline-carboxylic acid:EP 1160241
N-[[3-[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide:154590-43-9: US 5547950

EXAMPLE 12: 7-[4-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



1-(1-Benzyl-piperidin-4-yl)-4-(2-fluoro-4-nitro-phenyl)-piperazine
To a solution of 10 g of 2,2-[(2-fluoro-4-nitrophenyl)-imino]bis-ethanol (40.5 mmol) and 12.3 g triethylamine (120 mmol) in 200 ml dichloromethane at 0°C were added 11.12 g methane sulfonylchloride (97.3 mmol). The reaction mixture was stirred at rt and monitored by TLC. The mixture was diluted with

50 ml dichloromethane, washed with water, sodium bicarbonate solution and brine at 0°C. The org. layer was dried over Mg sulfate, filtered and the filtrate evaporated to leave a yellow solid. The solid was dissolved in 200 ml toluene and 8.48g 4-amino-1-benzylpiperidine and 16.9 ml triethylamine were added. The suspension was stirred at 120°C for 72 hrs. The reaction was monitored by TLC. The solvents were evaporated, the residue dissolved in ethyl acetate, washed with water and brine, dried over MG sulfate, filtered and evaporated. The residue was purified by chromatography, using a 9/1 dichloromethane / methanol mixture as eluent. The interesting fractions were collected and evaporated. The residue was crystallized from ethyl acetate/hexane mixture.
Yield: 6.05 g, 40%. MW:398.48, (C22H27FN4O2) MS: 399.4 $(M+H)^+$, Method ESI^+.

4-[4-(4-Benzyloxycarbonylamino-2-fluoro-phenyl)-piperazin-1 yl]-piperidine-1-carboxylic benzyl ester.
To a solution of 6.05g 1-(1-benzyl-piperidin-4-yl)-4-(2-fluoro-4-nitro-phenyl)-piperazine (15.2 mmol) 50 ml methanol and 5 ml acetic acid was added 2 g of Pd/C 10%. The suspension was stirred mechanically under hydrogen. The reaction was monitored by TLC. The Pd/C was filtered, the filtrate evaporated to dryness. The residue was dissolved in 250 ml acetone, diluted with 125 ml of a saturated solution of sodium bicarbonate, and reacted with 8 ml of benzyl chloroformate. The reaction was monitored by TLC. The acetone was evaporated, the sticky oil dissolved in ethyl acetate, washed with water and brine and dried over Mg sulfate. The Mg sulfate was filtered and the filtrate evaporated to dryness. The residue was crystallized from an ethyl acetate/hexane mixture.
Yield: 6.40 g, 77%. MW:546.64, (C31H35FN4O4) MS: 547.4 $(M+H)^+$, Method ESI^+.

4-{4-[2-fluoro-4{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenyl]-piperazin-1-yl}-piperidin-1-carboxylic acid benzyl ester.

To a solution of 6.3 g 4-[4-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-piperazin-1-yl]-piperidine-1-carboxylic benzyl ester (11.52 mmol) in 60 ml of dry THF were added at -20°C under stirring 5.7 ml of a 2.25 M LDA solution (12.8 mmol) in THF. The reaction was allowed to warm up to 0°C, and 2.1 ml of R(-)-glycidyl butyrate (14.9 mmol) were added. The reaction was stirred at rt. and monitored by TLC. The reaction was quenched with ammonium chloride solution, diluted with water, and the org. layer was washed with 10% sodium bicarbonate solution and brine. The org. layer was dried over Mg sulfate and filtered. The filtrate was evaporated to dryness, and the residue crystallized from an ethyl acetate / hexane mixture.

Yield: 3.87 g, 65.5%. MW:512.58, ($C_{27}H_{33}FN_4O_5$) MS: 513.7 $(M+H)^+$, Method ESI^+.

4-{4-[4-{(5R)-5-Azidomethyl-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl]-piperazin-1-yl}-piperidin-1-carboxylic acid benzyl ester

To a solution of 3.67g 4-{4-[2-fluoro-4{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenyl]-piperazin-1-yl}-piperidin-1-carboxylic acid benzyl ester (7.16 mmol) and 1.99 ml of triethylamine (, 14.3 mmol) in 50 ml dichloromethane was added at 0°C 0.66 ml of methansulfonyl chloride (, 8.59 mmol). The reaction was stirred at room temperature and monitored by TLC. The reaction was diluted with water and washed with water and brine. The org. layer was dried over Mg sulfate, filtered and evaporated. The oily residue was dissolved in 15 ml DMF. 100 mg of tetrabutyl ammonium iodide and 0.930 g sodium azide (14.32 mmol) were added and the mixture stirred under nitrogen at 80°C. The reaction was monitored by TLC. The DMF was evaporated, the

residue dissolved in ethyl acetate and washed with water and brine. The org. layer was dried over Mg sulfate, filtered and evaporated. The residue was crystallized from an ethyl acetate/ether mixture.
Yield: 2.65 g, 69%. MW:537.59, (C27H32FN7O4) MS: 538.8 $(M+H)^+$, Method ESI^+.

4-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-piperidin-1-carboxylic acid benzyl ester.
A solution of 2.65g of 4-{4-[4-{(5R)-5-azidomethyl-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl]-piperazin-1-yl}-piperidin-1-carboxylic acid benzyl ester (4.93 mmol), 1.55 g triphenylphosphine (5.91 mmol) and 0.88 g water (49.3 mmol) in 40 ml THF was stirred at reflux for 22 hrs. The reaction was controlled by TLC. The THF was evaporated and the residue dissolved in 10 ml acetic acid and 2 ml of acetic anhydride. the reaction was monitored by TLC. The solvents were evaporated and the residue crystallized from ethyl acetate.
Yield: 2.57 g, 94%. MW:553.63, (C29H36FN5O5) MS: 554.5 $(M+H)^+$, Method ESI^+.

N-{(5S)-3-[3-Fluoro-4-(4-piperidin-4-yl-piperazin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide
A suspension of 500 mg of 10% Pd/C and 2.5 g 4-(4-{4-[(5R)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-piperidin-1-carboxylic acid benzyl ester(,5.51 mmol) in 50 ml methanol was stirred under hydrogen. The reaction was monitored by TLC. The Pd/C was filtered off, the filtrate evaporated to dryness and the residue digested in an ethyl acetate / hexane mixture. The glassy solid was filtered, washed with hexane and dried.

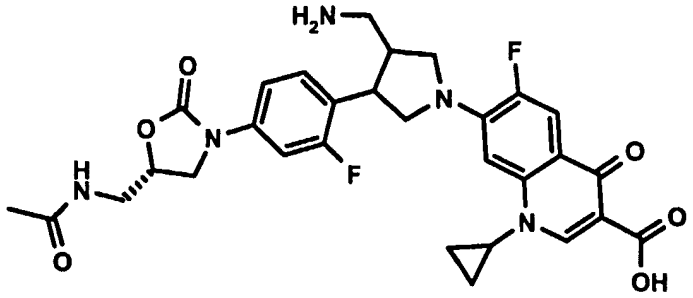
Yield: 1.805 g, 78%. MW:419.50, (C21H30FN5O3) MS: 420.5 $(M+H)^+$, Method ESI^+.

7-[4-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

A suspension of 130 mg 6,7-difluoro-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylatoboron diacetate (0.33 mmol), 147 mg N-{3-[3-fluoro-4-(4-piperidin-4-yl-piperazin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (0.35 mmol) and 56 mg DABCO (0.5 mmol) in 10 ml acetonitrile were heated under stirring in a micro wave oven at 150°C for 10 min. The solvents were evaporated, the residue digested over night in ethanol and the solid filtered off. The solid was digested in a 4/1 mixture of methanol / 1N HCl and the solid filtered.

Yield: 65 mg, 29%. MW:664.72, (C34H38F2N6O6) MS: 665.5 $(M+H)^+$, 663.4 $(M-H)^-$ Method ESI^+, ESI^-

EXAMPLE 13: 7-[(3R, 4R) and (3S, 4S)-3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-4-aminomethyl-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-3-carboxylic acid.



(4-Bromo-3-fluoro-phenyl)-carbamic acid benzyl ester

To a solution of 10g of 4-bromo-3-fluoroaniline (52 mmol) in 300 ml acetone were added successively 150 ml of a saturated sodium

bicarbonate solution and at 0°C 9 ml of benzyl chloroformate (63 mmol). The reaction was monitored by TLC. The acetone was evaporated, the residue extracted twice with ethyl acetate, washed with water and brine, dried and evaporated. The residue was crystallized from an ethyl acetate/ hexane mixture.
Yield: 15.7 g, 92%. MW:324.15, (C14H11BrFNO2) MS: 322.4 $(M-H)^-$ Method ESI^-.

3-(4-Benzyloxycarbonylamino-2-fluoro-phenyl)-acrylic acid ethyl ester
A suspension of 9.72 g (4-bromo-3-fluoro-phenyl)-carbamic acid benzyl ester (30 mmol), 6g ethyl acrylate (60 mmol), 10.2 ml DIPEA (60 mmol), 112mg palladium acetate (, 3 mmol), and 1.57 g triphenylphosphine (6 mmol) in 10 ml DMF were stirred at 130 °C for 48h. The reaction was monitored by TLC. The DMF was evaporated, the residue dissolved in dichloromethane, washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated. The residue was purified by chromatography, using a 7/3 N-hexane/ethyl acetate mixture as eluent.
Yield: 4.50 g, 43%. MW:343.35, (C19H18FNO4) MS: 342.1 $(M-H)^-$ Method ESI^-.

(3S, 4R) and (3R, 4S)-1-Benzyl-4-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-pyrrolidine-3-carboxylic acid ethyl ester.
To a solution of 4.5 g of 3-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-acrylic acid ethyl ester (, 13.1 mmol) and 7.68 g N-[(pentyloxy)methyl]-N-[(trimethylsilyl)-methyl]-benzenemethanamine (26.2 mmol) in 50 ml dichloromethane was added 10 µL. trifluoroacetic acid. The reaction was monitored by TLC. The reaction was complete after 10 min. The mixture was diluted with dichloromethane, washed with sat. sodium bicarbonate solution and brine, dried over Mg sulfate, filtered and the filtrate evaporated. The residue was purified by

filtration over a short silica column, using a 7/3 hexane /ethyl acetate mixture as eluent.
Yield: 4.93g, 79%. MW:476.55, ($C_{28}H_{29}FN_2O_4$) MS: 477.4 $(M+H)^+$ Method ESI^+.

[4-{(3R, 4S) and (3S,4R)-1-Benzyl-4-hydroxymethyl-pyrrolidin-3-yl}-3-fluoro-phenyl] -carbamic acid benzyl ester.
A solution of 4.05 g (3R ,4S) and (3S, 4R)-1-benzyl-4-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-pyrrolidine-3-carboxylic acid ethyl ester (, 10.3 mmol) in 10 ml ether was added to a suspension of 480 mg LAH (15.5 mmol) in 100 ml diethylether at RT. The reaction was monitored by TLC. The excess LAH was hydrolyzed by a saturated sodium/potassium tartrate salt solution. The reaction was diluted with ethyl acetate, washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated to dryness. The residue was crystallized from an ethyl acetate / hexane mixture.
Yield: 4.93g, 79%.MW:434.51, ($C_{26}H_{27}FN_2O_3$) MS: 435.6 $(M+H)^+$ Method ESI^+.

[4-{(3R, 4S) and (3S, 4R)-4-Azidomethyl-1-benzyl-pyrolidin-3-yl}-3-fluoro-phenyl]-carbamic acid benzyl ester.
This compound was synthesized in analogy to the procedure described in Example 12 with 4.73 g [4-{(3R,4S) and (3S,4R)-1-benzyl-4-hydroxymethyl-pyrrolidin-3-yl}-3-fluoro-phenyl]-carbamic acid benzyl ester (10.9 mmol)
Yield: 5.0 g, quantitative. MW:459.52, ($C_{26}H_{26}FN_5O_2$) MS: 460.6 $(M+H)^+$ Method ESI^+.

{4-[(3R, 4S) and (3S, 4R)-1-Benzyl-4(*tert*-butoxycarbonyl-aminomethyl)-pyrrolidin-3-yl]-3-fluoro-phenyl}-carbamic acid benzyl ester.

A solution of [4-{(3R,4S) and (3S,4R)-4-azidomethyl-1-benzyl-pyrolidin-3-yl}-3-fluoro-phenyl]-carbamic acid benzyl ester (10.3 mmol), 3.39 g triphenylphosphine (12.96 mmol) and 1.8g H2O (MW:18,0 100 mmol) in 80 ml THF was stirred at reflux for 22 hrs. The reaction was controlled by TLC. 2.25 ml triethylamine (16.2 mmol) and 2.82 g BOC_2O (12.9 mmol) were added and the mixture stirred at rt. The reaction was monitored by TLC. The solvent was evaporated and the residue was purified by chromatography, using an ethyl acetate /hexane 7/3 mixture as eluent.
Yield: 5.0 g, quantitative. MW:533.64, (C31H36FN3O4) MS: 534.4 $(M+H)^+$ Method ESI^+.

{(3R, 4S) and (3S, 4R)-1-Benzyl-4-[2-fluoro-4-{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenyl]-pyrrolidin-3-ylmethyl}-carbamic acid *tert*-butyl ester.
This compound was synthesized in analogy to the procedure described in Example 12 with 4.45 g {4-[(3R, 4S)and (3S, 4R)-1-benzyl-4 (*tert*-butoxycarbonylamino-methyl)-pyrrolidin-3-yl]-3-fluoro-phenyl}-carbamic acid benzyl ester (8.33 mmol)
Yield: 2.65 g, 63.6%. MW:499.58, (C27H34FN3O5) MS: 500.4, $(M+H)^+$ Method ESI^+.

{(3R, 4S) and (3S, 4R)-1-Benzyl-4-[2-fluoro-4-{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenyl]-pyrrolidin-3-ylmethyl}-carbamic acid *tert*-butyl ester.
This compound was synthesized in analogy to the procedure described in Example 12 with 2.60 g{(3R, 4S)and (3S, 4R)-1-benzyl-4-[2-fluoro-4-{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenyl]-pyrrolidin-3-ylmethyl}-carbamic acid *tert*-butyl ester (5.20 mmol)
Yield: 2.70 g, quantitative. MW:524.6, (C27H33FN6O4) MS: 525.6, $(M+H)^+$ Method ESI^+.

[(3R-4S) and (3S-4R)-4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-1-benzyl-pyrrolidin-3-ylmethyl]-carbamic acid *tert*-butyl ester.

This compound was synthesized in analogy to the procedure described in Example 9 with 2.7 g {(3R, 4S)and (3S, 4R)-1-benzyl-4-[2-fluoro-4-{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenyl]-pyrrolidin-3-ylmethyl}-carbamic acid *tert*-butyl ester (5.20 mmol)

Yield: 2.54 g, 90%. MW:540.64, ($C_{29}H_{37}FN_4O_5$) MS: 541.3, $(M+H)^+$ Method ESI^+.

[(3R, 4S) and (3S, 4R)-4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-pyrrolidin-3-ylmethyl]-carbamic acid *tert*-butyl ester.

This compound was synthesized in analogy to the procedure described in Example 12 with 2.5 g [(3R, 4S)and (3S, 4R)-4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-1-benzyl-pyrrolidin-3-ylmethyl]-carbamic acid *tert*-butyl ester (4.6 mmol)

Yield: 1.69 g, 81%. MW:450.51, ($C_{22}H_{31}FN_4O_5$) MS: 451.5, $(M+H)^+$ Method ESI^+.

7-[(3R, 4R) and (3S, 4S)-3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-4-aminomethyl-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-3-carboxylic acid.

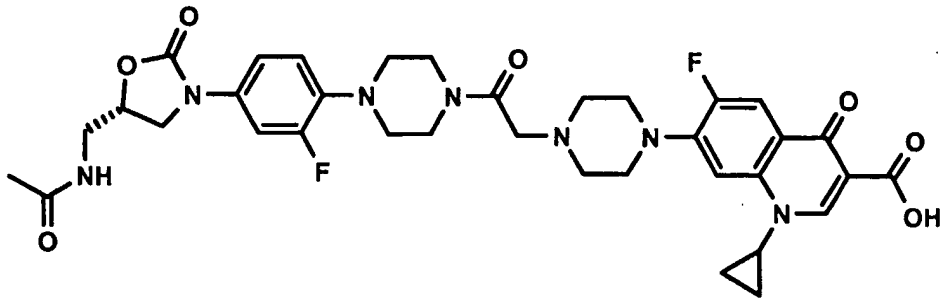
A suspension of 130 mg 6,7-difluoro-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylatoboron diacetate (MW: 393.11.0.33 mmol), 163 mg [(3R-4S) and (3S-4R)-4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-pyrrolidin-3-ylmethyl]-carbamic acid *tert*-butyl ester (0.36 mmol) and 56 mg DABCO (0.5 mmol) in 10 ml acetonitrile were heated under

stirring with in microwave oven at 150°C for 10 min. The reaction was monitored by TLC. The acetonitrile was evaporated, the residue dissolved in 3 ml methanol and treated with 3 ml 1.25 M HCl in methanol. The reaction was stirred for 20 h and purified by preparative HPLC.

Yield: 75 mg, 36 %. MW:595.61, (C30H31F2N5O6)

MS: 596.5, $(M+H)^+$ Method ESI^+.

EXAMPLE 14: 7-{4-[2-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-2-oxo-ethyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolone-3-carboxylic acid:



4-[2-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-2-oxo-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester.

To a stirred suspension of 672 mg of N-[(5S)-3-(3-fluoro-4-piperazine-1-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide (2 mmol) and 0.42 ml of triethylamine (3 mmol) in 30 ml dichloromethane was added at rt. a solution of 484 mg bromoacetylbromide (2.4 mmol) in 2 ml of dichloromethane. The reaction was monitored by TLC. The reaction solution was washed with water and brine, the dichloromethane layer dried over Mg sulfate, filtered and the filtrate evaporated to dryness. The residue was digested in 20 ml ether, the solid filtered and dried. The colorless solid was dissolved in 10 ml DMF, 372 mg N-

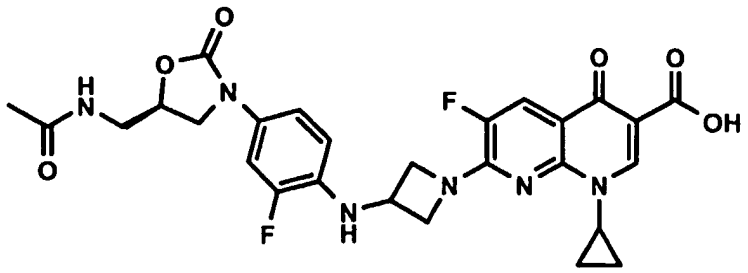
Boc piperazine 2 mmol) and 276 mg of potassium carbonate (2 mmol)were added. The reaction was stirred over night at 60°C and monitored by TLC. The DMF was evaporated to dryness, the residue purified by chromatography, using a 19/1 dichloromethane/methanol mixture as eluent.
Yield: 0.494 g, 44 %. MW:562.64, (C27H39FN6O6)
MS: 563.5 $(M+H)^+$, Method ESI^+.

N-[(5S)-3-{3-Fluoro-4[4-(2-piperazin-1-yl-acetyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl]-acetamide.
A solution of 0.490g of 4-[2-(4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-2-oxo-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester (0.87 mmol) in 2 ml dichloromethane was treated with 2 ml of TFA. The reaction was monitored by TLC. The solvent was evaporated and the residue dissolved in water. The water layer was neutralized with ammonium hydroxide and freeze-dried.
Yield: 0.494 g, 44 %. MW:462.52, (C22H31FN6O4)
MS: 463.6 $(M+H)^+$, Method ESI^+.

7-{4-[2-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-2-oxo-ethyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolone-3-carboxylic acid.
A suspension of 169 mg 6,7-difluoro-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylatoboron diacetate (0.33 mmol), 198 mg N-[(5S)-3-{3-fluoro-4[4-(2-piperazin-1-yl-acetyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl]-acetamide (0.43 mmol), and 120 mg DABCO (1.07 mmol), in 10 ml acetonitrile was stirred at 150°C in a micro wave oven for 10 min. The reaction was monitored by TLC. The acetonitrile was evaporated, the residue dissolved in 3 ml methanol and treated with 3 ml 1.25 M

HCl in methanol. The reaction was stirred over night, and the solid filtered off. The solid was purified by prep HPLC.
Yield: 29 mg, 9.6 %. MW:707.74, (C35H39F2N7O7)
MS: 708.7, $(M+H)^+$, 706.6, $(M-H)^-$, Method ESI^+, ESI^-.

EXAMPLE 15: 7-(3-{4-[5(S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-azetidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



(1-Benzhydryl-azetidin-3-yl)-(2-fluoro-4-nitro-phenyl)-amine.
A solution of 7.96 g of 1-benzhydrylazetidin-3-ylamine (33,41 mmol), 3.69 ml 3.4-difluoronitrobenzene (33.41 mmol) and 4.65ml triethylamine (33.41 mmol)) in 50 ml ethyl acetate was stirred for 2 weeks at 60°C. The reaction was diluted with water and the product extracted with ethyl acetate. The organic layer was washed with water and brine, dried over MgSO4, filtered and evaporated.
Yield: 13.2 g, quantitative. MW:393.46, (C23H24FN3O2)
1H-NMR (δ ppm DMSO-d_6): 2.78 (m, 2H, CH_2); 3.54 (m, 2H, CH_2); 4.02 (m, 1H, CH); 4.46 (s, 1H, CH); 6.69 (t, 1H, aro); 7.1-7.5 (m,8H, biphenyl); 7.90 (m, 2H, aro)

3-[(Benzyloxycarbonyl-(4-benzyloxycarboylamino-2-fluoro-phenyl)-amino]-azetidine-1-carboxylic acid benzyl ester.

A suspension of 1 g of (1-benzhydryl-azetidin-3-yl)-(2-fluoro-4-nitro-phenyl)-amine (2.54 mmol) and 200mg Pd/C 10% in 10 ml of a methanol with 5 % acetic acid mixture was stirred under H_2 for 20 hrs . The Pd/C was filtered off and the filtrate evaporated. The oily residue was digested in hexane, and decanted in order to eliminate the hexane soluble biphenylmethane. MS 182 $(M+H)^+$, Method ESI^+. The remaining sticky oil was dissolved in 10 ml acetone. 10.0 ml of a saturated solution of sodium bicarbonate and 1.25 ml benzyl chloroformate (7.62mmol) were added at 0°C. The mixture was stirred for 4 h at RT. The acetone was evaporated, and the residue diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated. The residue was purified by chromatography using an ethyl acetate /hexane 4/5 mixture as eluent.

Yield: 916 mg, 63%. MW:583.62, ($C_{33}H_{30}FN_3O_6$)

MS: 584.5 $(M+H)^+$, Method ESI^+.

3-{Benzyloxycarbonyl-[2-fluoro-4-{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenyl]-amino}-azetidine-1-carboxylic acid benzyl ester.

To a solution of 0.916g of 3-(benzyloxycarbonyl-(4-benzyloxycarboylamino-2-fluoro-phenyl)-amino]-azetidine-1-carboxylic acid benzyl ester (1.56 mmol) in 5 ml THF were added at -15°C 0.767 ml of a 2.25M LDA (1.7 mmol) solution in THF. The mixture was allowed to warm up to 0°C and stirred for 5 min. Then, 0.26 ml of (R)-glycidyl butyrate (1.87 mmol) was added and the yellow solution was stirred for 2 h at RT. The reaction was quenched with a saturated solution of ammonium chloride. The mixture was diluted with ethyl acetate, the org. layer washed with water and brine and dried over Mg sulfate. The residue was purified by chromatography using a 95/5 dichloromethane / methanol mixture as eluent.

Yield: 377 mg, 43 %. MW:549.56, ($C_{29}H_{28}FN_3O_7$) MS: 550.7 $(M+H)^+$, Method ESI^+

3-{[4-{(5R)-5-Azidomethyl-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl]-benzyloxycarbonyl-amino)-azetidine-1-carboxylic acid benzyl ester.

To a solution of 1.08 g 3-{benzyloxycarbonyl-[2-fluoro-4-{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenyl]-amino}-azetidine-1-carboxylic acid benzyl ester (2 mmol) in 20 ml dichloromethane was added at 0°C 0.56 ml triethylamine (4 mmol) and 0.17 ml methanesulfonyl chloride (2.2 mmol). The reaction was stirred at RT for 1 hr and quenched with water. The organic layer was washed with brine, dried with Mg sulfate, filtered and the filtrate evaporated. Yield: 391 mg, 90%. Ms 584.0 $(M+H)^+$, Method ESI^+.

A suspension of the intermediate, 260 mg sodium azide (65.01, 4 mmol) and 37 mg tetrabutylammonium iodide (0.1mmol) in 15 ml DMF was stirred at 80°C for 16 h. The DMF was evaporated. The residue was diluted with water and ethyl acetate. The org. layer was washed with brine, dried over Mg sulfate, filtered and the filtrate evaporated.

Yield: 1,15 g, 93 %.MW:574.57, ($C_{29}H_{27}FN_6O_6$) MS: 575.4 $(M+H)^+$, Method ESI^+

3-({4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-benzyloxycarbonyl-amino)-azetidine-1-carboxylic acid benzyl ester.

A solution of 1.15 g 3-{[4-{(5R)-5-azidomethyl-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl]-benzyloxycarbonyl-amino)-azetidine-1-carboxylic acid benzyl ester (2 mmol), 0.36 ml water (20 mmol) and 0.277 g triphenylphosphine (2.2 mmol) was stirred for 16 h at 50°C. The solvent was evaporated. The residue was dissolved in 5 ml acetic acid and 2 ml acetic anhydride. The solution was

stirred for 30 min and evaporated. The residue was purified by chromatography using a 9/1 ethyl acetate /methanol mixture as eluent.

Yield: 1.1 g, 93 %. MW:590.61, (C31H31FN4O7)

MS: 547.4 $(M+H)^+$, 546.5$(M-H)^-$, Method ESI^+, Method ESI^-

N-{(5S)-3-[4-(Azetidin-3-ylamino)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide

A suspension of 1.11 g of 3-({4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-benzyloxycarbonyl-amino)-azetidine-1-carboxylic acid benzyl ester (1.88 mmol) and 200 mg Pd/c 10% in methanol was stirred under hydrogen for 5 h. The Pd/C was filtered and the filtrate evaporated to dryness.

Yield: 340 mg, 56 %. MW:322.34, (C15H19FN4O3); MS: 323.5 $(M+H)^+$, Method ESI^+

7-(3-{4-[5(S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-azetidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid.

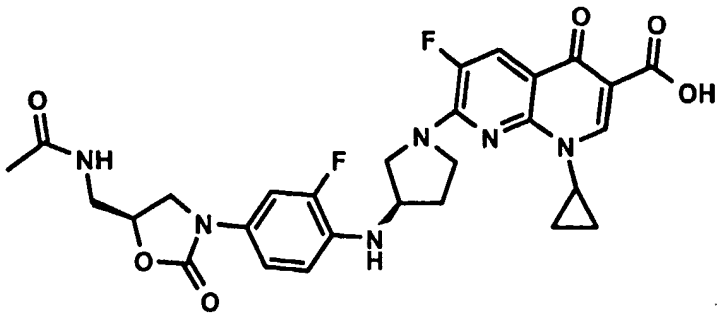
A solution of 85mg of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid 0.3 mmol), 97mg N-{(5S)-3-[4-(azetidin-3-ylamino)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (0.3 mmol), 40 mg triethylamine (0.4 mmol) and 0.065 ml trimethylchlorosilane (0.6 mmol) in 2 ml DMSO was heated at 150°C under stirring in a microwave oven for 10 min. The reaction was monitored by HPLC. The DMSO was evaporated, the residue digested in water, filtered and the solid purified by chromatography, using a 95/5 dichloromethane / methanol mixture as eluent.

Yield: 52 mg, 30 %.MW:568.54, (C27H26F2N6O6) MS: 569 $(M+H)^+$, Method ESI^+

Known building block:

1-benzhydrylazetidin-3-ylamine, 40432-52-8, Beta Pharma Catalog

EXAMPLE 16: 7-[(3R)-3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]-naphthyridine-3-carboxylic acid:



7-[(3R)-3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid

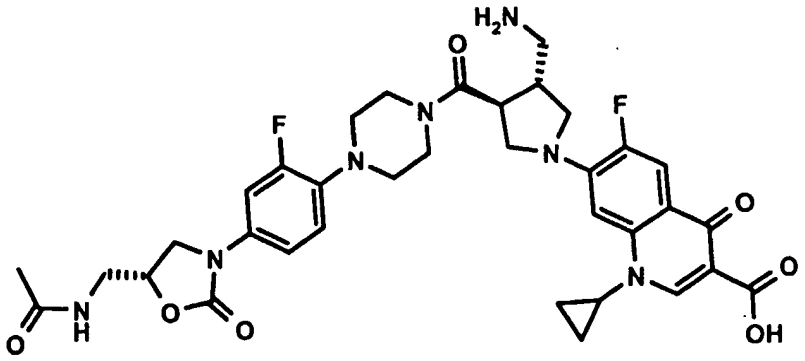
A suspension of 119 mg N-{(5S)-3-[3-fluoro-4-(pyrrolidin-3-ylamino)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (0.35 mmol), 100 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 148 µl triethylamine (,1.05 mmol) and 89 µl trimethylchlorosilane (0.70 mmol) in 2 ml DMSO was stirred in a microwave oven at 150°C for 10 min. The DMSO was evaporated, the residue digested in water and the solid filtrated. The solid was purified by chromatography using a 95/5 dichloromethane / methanol mixture.

Yield: 10 mg, 5%. MW:582.56, (C28H28F2N6O6) MS: 583.2 $(M+H)^+$, Method ESI^+

Known buiding blocks:

- 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-Naphthyridine-3-carboxylic acid: CAS 100361-18-0, Louston International.

EXAMPLE 17: 7-[(3R, 4S) and (3S, 4R)-3-(-4{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}piperazine-1-carbonyl)-4-aminomethyl-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline carboxylic acid



(3R, 4R) and (3S, 4S)-1-Benzyl-4-(*tert*-butoxycarbonylamino-methyl)-pyrrolidine-3-carboxylic acid ethyl ester.

To a solution of 2 g of 4-tert-butoxycarbonylamino-but-2-enoic acid ethyl ester (8.72 mmol) and 5.12 g N-[(pentyloxy)methyl]-N-[(trimethylsilyl)methyl]- benzene-methanamine (17.4 mmol) in 50 ml dichloromethane was added 10 micro-l. trifluoroacetic acid .The reaction was monitored by TLC. The reaction was complete after 10 min. The mixture was diluted with dichloromethane, washed with sat. sodium bicarbonate solution and brine, dried over Mg sulfate, filtered and the filtrate evaporated. The residue was purified by filtration over a short silica column, using a 7/3 hexane / ethyl acetate mixture as eluent.

Yield: 2.96 g, 93 %. MW:362.47, (C20H30N2O4) MS: 363.6 $(M+H)^+$, Method ESI^+.

(3R, 4R) and (3S, 4S)-1-Benzyl-4-(*tert*-butoxycarbonylamino-methyl)-pyrrolidine-3-carboxylic acid.

To a solution of 2.9 (3R, 4R) and (3S, 4S)-1-benzyl-4-(*tert*-butoxycarbonylamino-methyl)-pyrrolidine-3-carboxylic acid ethyl ester (8.0 mmol) in 50 ml THF were added 671 mg lithium hydroxide mono hydrate (, 16 mmol) and 0.5 ml water. The solution was stirred at 40°C and the reaction monitored by TLC. After 72 h the solvent was evaporated, the residue dissolved in dichloromethane, washed with water and brine, dried over Mg sulfate, filtered and evaporated. The residue was crystallized from a dichloromethane /hexane mixture.

Yield: 1.9 g, 71 %. MW:334.41, (C18H26N2O4) MS: 335.3 $(M+H)^+$, 333.3 $(M-H)^-$, Method ESI^+, ESI^-.

[(3R, 4R) and (3S, 4S)-4-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazine-1-carbonyl)-1-benzyl-pyrrolidin-3-ylmethyl]-carbamic acid *tert*-butyl ester.

To solution of 0.668 g of 1-benzyl-4-(*tert*-butoxycarbonyl-amino-methyl)-pyrrolidine-3-carboxylic acid (2 mmol), 0.6 ml triethylamine (4 mmol), and 0.662 g N-[{(5S)-3[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl}methyl]-acetamide (2 mmol) in 50 ml dry DMF was added 0.796 g of O-(benzotriazol-1-yl)-N, N, N´, N´-tetramethyluronium-hexafluorophosphate (252.1 mmol). The reaction was stirred at rt. for 20 hrs. The DMF was evaporated, the residue dissolved in ethyl acetate, washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated. The residue was purified by chromatography, using a 9/1 dichloromethane/methanol mixture as eluent.

Yield: 1.14 g, 87 %. MW:652.77, (C34H45FN6O6) MS: 653.7 $(M+H)^+$, Method ESI^+.

[[(3R, 4R) and (3S, 4S)-4-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazine-1-carbonyl)-pyrrolidin-3-ylmethyl]-carbamic acid *tert*-butyl ester.

A suspension of 1.1 g [(3R, 4R) and (3S, 4S)-4-(4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazine-1-carbonyl)-1-benzyl-pyrrolidin-3-yl-methyl]-carbamic acid *tert*-butyl ester (1.68 mmol) and 0.2 g Pd/C 10% in 10 ml methanol and 2 ml acetic acid was stirred under hydrogen. The reaction was monitored by TLC. The solvent was evaporated to leave an amorphous solid.

Yield: 1.14 g, 87 %. MW:562.64, (C27H39FN6O6) MS: 563.3,$(M+H)^+$, Method ESI^+.

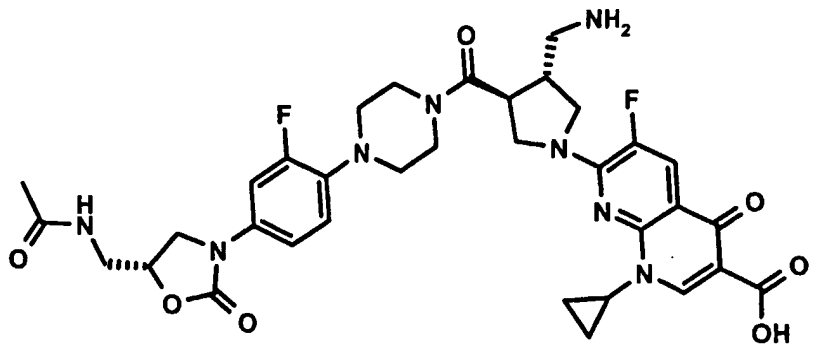
7-[(3R, 4S) and (3S, 4R)-3-(-4{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}piperazine-1-carbonyl)-4-aminomethyl-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline carboxylic acid.

A solution of 141 mg [[(3R, 4R) and (3S, 4S)-4-(4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazine-1-carbonyl)-pyrrolidin-3-ylmethyl]-carbamic acid *tert*-butyl ester (0.25 mmol), 102 mg 7-chloro-6-fluoro-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline-3-carboxylatoboron diacetate (0.25 mmol) and 61 mg DABCO (0.5 mmol) in 2 ml DMSO was stirred at 150°C for 12min in a microwave oven. The reaction was monitored by TLC. The DMSO was evaporated, the residue dissolved in acetonitrile, diluted with water and concentrated. The solid was filtered and purified by prep HPLC.

Yield: 20 mg, 11.3 %. MW:707.74, (C35H39F2N7O7) MS: 708.7, $(M+H)^+$, Method ESI^+

EXAMPLE 18: 7-[(3R, 4S) and (3S, 4R)-3-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-

piperazine-1-carbonyl)-4-aminomethyl-pyrrolidin-1-yl)1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid

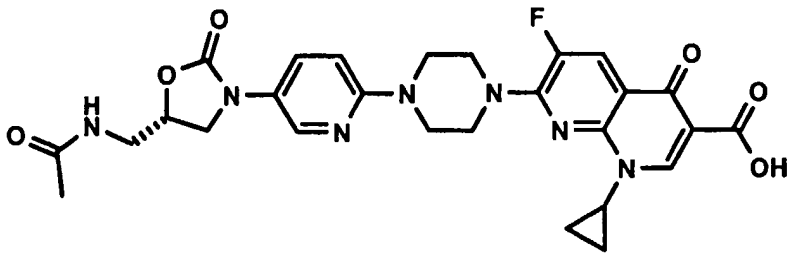


7-[(3R, 4S) and (3S, 4R)-3-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazine-1-carbonyl)-4-aminomethyl-pyrrolidin-1-yl)1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid.

A solution of 99 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (0.35 mmol), 197 mg [(3R, 4R)and (3S, 4S)-4-(4-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazine-1-carbonyl)-pyrrolidin-3-ylmethyl]-carbamic acid *tert*-butyl ester (0.35 mmol), 146 microL triethylamine (1.05 mmol) and 76 mg trimethylchlorsilane (0.70 mmol) were dissolved in 2 ml DMSO. The solution was heated at 150°C under stirring in a microwave oven for 10 min. The reaction was monitored by TLC. The DMSO was evaporated, the residue digested in water, filtered and the solid purified by chromatography, using dichloromethane / methanol mixture as eluent. The intermediate was crystallized from acetonitrile. The crystals were dissolved in a 1.25 M HCl and stirred at rt. The reaction was monitored by TLC. The methanol was evaporated and the residue purified by preparative HPLC.

Yield: 130 mg, 52 %. MW:708.72, ($C_{34}H_{38}F_2N_8O_7$) MS: 709.6,$(M+H)^+$, Method ESI^+.

EXAMPLE 19: 7-(4-{5-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-pyridin-2-yl}-1-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



4-(Benzyloxycarbonylamino-pyridin-2-yl)-piperazine-1-carboxylic acid *tert*-butyl ester.

To a solution of 4 g 4-(5-nitro-pyridin-2-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (12.9 mmol) in 50 ml ethyl acetate and 50 ml methanol was added 0.5 g Pd/C 10%. The suspension was stirred under a hydrogen atmosphere. The reaction was monitored by TLC. The Pd/C was filtered, the filtrate evaporated to dryness, the residue dissolved in 150 ml acetone, diluted with 75 ml of a saturated solution of sodium bicarbonate, and reacted with 2.65 g of benzyl chloroformate (15.56 mmol).The reaction was monitored by TLC. The acetone was evaporated, the residue dissolved in ethyl acetate, the org. layer washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated to dryness. The residue was crystallized from an ethyl acetate/hexane mixture.

Yield: 4.79 g, 89 %.MW:412.49, ($C_{22}H_{28}N_4O_4$) MS: 413.4, $(M+H)^+$, Method ESI^+.

4-[(5R)-5-(Hydroxymethyl-2-oxo-oxazolidin-3-yl)-pyridin-2-yl]-piperazine-1-carboxylic acid *tert*-butyl ester.

To a stirred solution of 4.69 g 4-(benzyloxycarbonylamino-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester (11.37 mmol) in 50 ml of THF at -70 C was added 7.46 ml of a 1.6M n-BuLi solution in N-hexane (11.93 mmol). The mixture was stirred at 0 C for 15 min, and 2.06 ml of R(-)-glycidyl butyrate (14.7 mmol) was added. The reaction was monitored by TLC. The reaction was then quenched with a saturated solution of ammonium chloride, diluted with ethyl acetate and washed with water and brine. The org. layer was dried over Mg sulfate, filtered and the filtrate evaporated to dryness. The residue was purified by chromatography, using an ethyl acetate/dichloromethane 9/1 mixture as eluent.
Yield: 2.58 g, 60 %. MW:378.43, (C18H26N4O5) MS: 379.6 $(M+H)^+$, Method ESI^+.

4-[(5R)-5-(Azidomethyl-2-oxo-oxazolidin-3-yl)-pyridin-2-yl]piperazine-1-carboxylic acid *tert*-butyl ester.
This compound was synthesized in analogy to the procedure described in Example 12 using 2.5 g 4-[(5R)-5-(hydroxymethyl-2-oxo-oxazolidin-3-yl)-pyridin-2-yl]-piperazine-1-carboxylic acid *tert*-butyl ester (6.62 mmol).
Yield:2.3 g, 86%. MW:403.44, (C18H25N7O4) MS: 404.4, $(M+H)^+$, Method ESI^+.

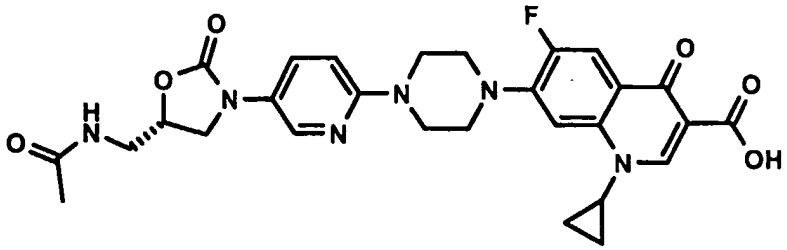
4-{5-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-pyridin-2-yl}-piperazine-1-carboxylic acid *tert*-butyl ester.
A suspension of 2.25 g of 4-[(5R)-5-(azidomethyl-2-oxo-oxazolidin-3-yl)-pyridin-2-yl]piperazine-1-carboxylic acid *tert*-butyl ester (6.62 mmol), and Pd/C 10% in methanol was stirred under hydrogen. The reaction was monitored by TLC. The solvent was evaporated and the residue dissolved in 10 ml acetic acid. 2ml of acetic anhydride were added to the solution and the reaction monitored by TLC. The solvent was evaporated and the

residue purified by chromatography, using a dichloromethane/methanol 9/1 mixture as eluent.
Yield: 0.572 g, 24 %. MW:419.48, (C20H29N5O5) MS: 420.4, $(M+H)^+$, Method ESI^+.

N-[(5S)-2-oxo-3-(6-piperazin-1-yl-pyridin-3-yl)-oxazolidin-5-ylmethyl]-acetamide.
0.54g of 4-{5-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-pyridin-2-yl}-piperazine-1-carboxylic acid *tert*-butyl ester (1.28 mmol) was dissolved in a 1.25 M HCl solution in methanol. The solution was stirred and the reaction monitored by TLC. The methanol was evaporated, the residue dissolved in water, neutralized with sodium bicarbonate and the water evaporated to dryness. The residue was digested in a 9/1 dichloromethane/methanol. The insoluble salt was filtered off, the filtrate evaporated to dryness to leave a pale brown solid.
Yield: 0.381 g, 93%. MW:3198.36, (C15H21N5O3) MS: 320.1, $(M+H)^+$, Method ESI^+.

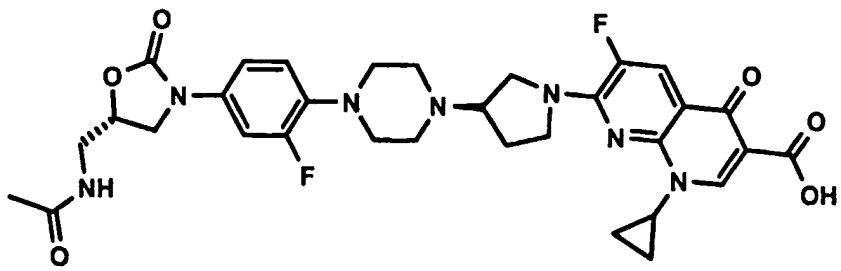
7-(4-{5-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-pyridin-2-yl}-1-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid.
This compound was synthesized in analogy to the procedure described in Example 10 using 0.135 g N-[2-oxo-3-(6-piperazin-1-yl-pyridin-3-yl)-oxazolidin-5-ylmethyl]-acetamide (0.42 mmol) and 120 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (0.42 mmol)
Yield:0.113 g, 47%. MW:565.57, (C27H28FN7O6) MS: 566.8, $(M+H)^+$; 564.8, $(M-H)^-$, Method ESI^+, ESI^-.

EXAMPLE 20: 7-(4-{5-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-pyridin-2-yl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.



A solution of 127 mg (S)-N-[2-oxo-3-(6-piperazin-1-yl-pyridin-3-yl)-oxazolidin-5-ylmethyl]-acetamide (0.4 mmol), 163 mg 7-chloro-6-fluoro-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline-3-carboxylatoboron diacetate (0.4 mmol) and 90 mg DABCO in 2 ml DMSO was stirred at 150 °C for 12 min. in a microwave oven. The reaction was monitored by TLC. The DMSO was evaporated, the residue digested in water. The solid was filtered and purified by chromatoghraphy, using dichloromethane /methanol as eluent. Yield:0.027 g, 11.9%. MW:564.58, (C28H29FN6O6) MS: 565.8 $(M+H)^+$, 563.6 $(M-H)^-$, Method ESI^+, ESI^-.

EXAMPLE 21: 7-[(3R)-3-(4-{4[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



(3R)-3-[4-(2-Fluoro-4-nitro-phenyl)-piperazin-1-yl]-pyrrolidine-1-carboxylic acid allyl ester.

This compound was synthesized in analogy to the procedure described in Example 12 using (3R)-3-amino-pyrrolidine-1-carboxylic acid allyl ester (1.28 mmol) and 2,2-[(2-fluoro-4-nitrophenyl)imino]bis-ethanol (40.5 mmol)

Yield: 3.38 g, 32%. MW:378.40, ($C_{18}H_{23}FN_4O_4$) MS: 379.5, $(M+H)^+$, Method ESI^+.

(3R)-3-[4-(2-Fluoro-4-nitro-phenyl)-piperazin-1-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

To a solution of 3.33 g (3R)-3-[4-(2-fluoro-4-nitro-phenyl)piperazin-1-yl]pyrrolidine-1-carboxylic acid allyl ester (8.8 mmol) in 60 ml THF were added 130 mg of bis (triphenylphosphine)-palladium(II) dichloride (0.088 mmol), 1.0 ml acetic acid (17.6 mmol), and 4.66 ml tributyl tinnhydride (17.6 mmol). The reaction was stirred at rt for 1 h and monitored by TLC. The suspension was diluted with 100 ml ether and a pale yellow solid precipitated. The solid was filtered, washed with ether and hexane and dried. The solid was diluted with 100 ml dichloromethane, 2.30 g BOC anhydride (MW: 218.25, 17.6 mmol) was added and the reaction stirred at RT over night and monitored by TLC. The reaction was diluted with dichloromethane, the org. layer washed with water and brine dried over Mg sulfate and filtered. The filtrate was evaporated. The residue was purified by chromatography, using ethyl acetate as eluent.

Yield: 0.740 g, 21%. MW:394.44, ($C_{19}H_{27}FN_4O_4$) MS: 395.3, $(M+H)^+$, Method ESI^+.

(3R)-3-[4-(4-Benzyloxycarbonylamino-Fluoro-phenyl)-piperazin-1-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

This compound was synthesized in analogy to the procedure described in Example 19 using 0.780 g (3R)-3-[4-(2-fluoro-4-nitro-phenyl)-piperazin-1-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.97 mmol).
Yield: 0.768 g, 78%. MW:498.6, (C27H35FN4O4) MS: 499.7, $(M+H)^+$, Method ESI^+.

(3R)-3-{4-[2-Fluoro-4-{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenyl]-piperazin-1-yl}-pyrrolidine-1-carboxylic acid tert-butyl ester.
This compound was synthesized in analogy to the procedure described in Example 19 using 0.780 g (3R)-3-[4-(4-benzyloxycarbonylamino-fluoro-phenyl)-piperazin-1-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.54 mmol).
Yield: 0.475 g, 66%. MW:464.54, (C23H33FN4O5) MS: 465.4, $(M+H)^+$, Method ESI^+.

(3R)-3-{4-[4-{(5R)-5-Azidomethyl-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl]-piperazin-1-yl}-pyrrolidine-1-carboxylic acid tert-butyl ester.
This compound was synthesized in analogy to the procedure described in Example 19 using 0.475 g (3R)-3-{4-[2-fluoro-4-{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenyl]-piperazin-1-yl}-pyrrolidine-1-carboxylic acid tert-butyl ester (1.02 mmol).
Yield: 0.500 g, quantitative. MW:489.55, (C23H32FN7O4) MS: 490.4, $(M+H)^+$, Method ESI^+.

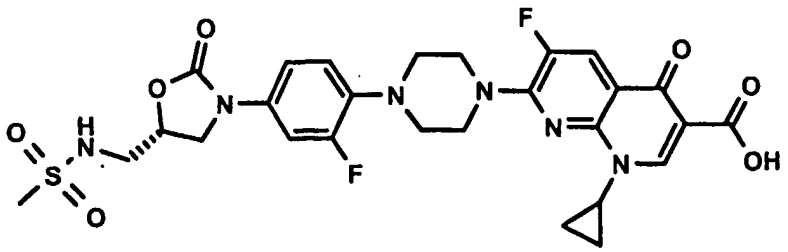
(3R)-3-{4-[4-{(5S)-5-Acetylaminomethyl-2-oxo-oxazolidin-3-yl}2-fluoro-phenyl]-piperazin-1-yl}-pyrrolidine-1-carboxylic acid tert-butyl ester.
This compound was synthesized in analogy to the procedure described in Example 19 using 0.475 g (3R)-3-{4-[4-{(5R)-5-

azidomethyl-2-oxo-oxazolidin-3-yl}2-fluoro-phenyl]-piperazin-1-yl}-pyrrolidine-1-carboxylic acid tert-butyl ester (1.02 mmol).
Yield: 0.398 g, 77%. MW:505.59, (C25H36FN5O5) MS: 506.4, $(M+H)^+$, Method ESI^+.

N-{(5S)-3-[3-Fluoro-4-(4-{(3R)-pyrrolidin-3-yl}-piperazin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide.
This compound was synthesized in analogy to the procedure described in Example 19 using 0.398 g (3R)-3-{4-[4-{(5S)-5-acetylaminomethyl-2-oxo-oxazolidin-3-yl}2-fluoro-phenyl]-piperazin-1-yl}-pyrrolidine-1-carboxylic acid tert-butyl ester (0.79 mmol).
Yield: 0.398 g, 77%. MW:405.47, (C20H28FN5O3) MS: 406.8, $(M+H)^+$, Method ESI^+.

7-[(3R)-3-(4-{4[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid.
This compound was synthesized in analogy to the procedure described in Example 19 using 0.0 90 g N-{(5S)-3-[3-fluoro-4-(4-{(3R)-pyrrolidin-3-yl}-piperazin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (0.22 mmol) and 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (0.22 mmol).
Yield: 47 mg, 32 %. MW:651.68, (C32H35F2N7O6) MS: 652.5, $(M+H)^+$; 650.8, $(M-H)^-$, Method ESI^+, ESI^-.

EXAMPLE 22: 1-Cyclopropyl-6-fluoro-7-(4-{2-fluoro-4-[(5R)-5-(methansulfonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid.



4-{2-Fluoro-4-[(5R)-5-(methansulfonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-carboxylic acid *tert*-butyl ester.

This compound was synthesized in analogy to the procedure described in Example 9 using 4-[4-{(5S)-5-aminomethyl-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (1.5 mmol)

Yield: 0.505 g, 71%. MW:472.53, ($C_{20}H_{29}FN_4O_6S$) MS: 473.4, $(M+H)^+$; 471.7, $(M-H)^-$, Method ESI^+, ESI^-.

N-[(5R)-3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-methansulfonamide.

This compound was synthesized in analogy to the procedure described in Example 19 using 0.5g 4-{2-fluoro-4-[(5R)-5-(methansulfonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-carboxylic acid *tert*-butyl ester (1.06 mmol).

Yield: 0.39 g, quantitative. MW:372.42, ($C_{15}H_{21}FN_4O_4S$)

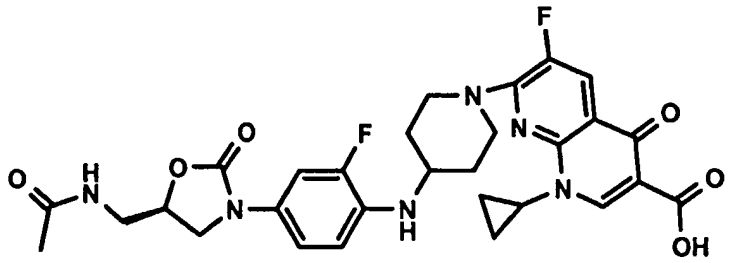
MS: 373.0, (M+H), Method ESI^+.

1-Cyclopropyl-6-fluoro-7-(4-{2-fluoro-4-[(5R)-5-(methan-sulfonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid.

This compound was synthesized in analogy to the procedure described in Example 10 using 0.082 g N-[(5R)-3-(3-fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-methansulfonamide (0.22 mmol) and 0.067g 7-chloro-1-

cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (0.22 mmol)
Yield: 0.079 g, 58 %.MW:618.62, (C27H28F2N6O7S) MS: 619.8, $(M+H)^+$; 617.7,$(M-H)^-$, Method ESI^+, ESI^-.

EXAMPLE 23: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



(1-Benzyl-piperidin-4-yl)-(2-fluoro-4-nitro-phenyl)-amine
9.54 g (MW: 159.09, 60 mmol) 3,4-difluorobenzene, 11.4 g (60 mmol) 4-amino-N-benzylpiperidine and 9.1 66 mmol) triethylamine in acetonitrile were stirred at reflux for 16 h. The solution was diluted with EtOAc, washed with water, and brine, dried over $MgSO_4$ and filtrated. The filtrate was evaporated, and the crystals were recrystallized with an ETOAc/hexane mixture.
Yield: 13,5 g, 70 %. MW:329.37, (C18H20FN3O2) MS: 430.1$(M+H)^+$, Method ESI^+.

2-Fluoro-N'-piperidin-4-yl-benzene-1,4-diamine.
A mixture of 5 g (15 mmol) of (1-benzyl-piperidin-4-yl)-(2-fluoro-4-nitro-phenyl)-amine in MeOH / EtOAc with Pd/C 10 % was stirred under H2 at RT. The reaction was monitored by TLC. The Pd/C was filtered and the filtrate evaporated to dryness.

Yield: 3.2 g, quant. MW:209.26, ($C_{11}H_{16}FN_3$) MS: 210.3 $(M+H)^+$, Method ESI^+.

4-(4-Benzyloxycarbonylamino-2-fluoro-phenylamino)-piperidine-1-carboxylic acid benzyl ester.

To a mixture of 3.2 g (15 mmol) 2-fluoro-N'-piperidin-4-yl-benzene-1,4-diamine in 150 ml acetone, was added 75 ml of sat $NaHCO_3$, and 5.3 ml (37.5 mmol) benzyl chloroformate. It was stirred for 2 h, the acetone was evaporated, and the water layer extracted twice with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and the filtrate evaporated. The residue was purified by chromatography using a hex/EtOAc 1:1 mixture.

Yield: 1.5 g, quant. MW:477.54, ($C_{27}H_{28}FN_3O_4$) MS: 478.4 $(M+H)^+$, Method ESI^+.

4-[2-Fluoro-4-{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenylamino]-piperidine-1-carboxylic acid benzyl ester.

To a solution of 6.6 g (15 mmol) 4-(4-benzyloxycarbonylamino-2-fluoro-phenylamino)-piperidine-1-carboxylic acid benzyl ester in 50 ml THF at -78 °C was added dropwise 12,12 ml nBuli 1.6 M (19.5 mmol). The mixture was further stirred at this temperature for 10 min. The resulting yellow solution was allowed to reach -40 °C over 10 min. 3.0 ml (21 mmol) of (R)-glycidyl butyrate was then added and the solution was allowed to reach slowly RT and further stirred for 16 h. The reaction was quenched with a saturated ammonium chloride solution, diluted with 400 ml of EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by chromatography using a CH_2Cl_2 / MeOH 5% mixture

Yield: 2.58 g, 50 %. MW:443.47, ($C_{23}H_{26}FN_3O_5$) MS: 444.6 $(M+H)^+$, Method ESI^+.

4-[4-{(5R)-5-Azidomethyl2-oxo-oxazolidin-3-yl}-2-fluoro-phenylamino]-piperidine-1-carboxylic acid benzyl ester.

To a solution of 2.5g of 4-[2-fluoro-4-{(5R)-5-hydroxymethyl-2-oxo-oxazolidin-3-yl}-phenylamino]-piperidine-1-carboxylic acid benzyl ester (5.6 mmol) and 1.57 ml (11.2 mmol) triethylamine in 60 ml dichloromethane, was added at 0°C 0.48 ml methanesulfonyl chloride (6.16 mmol). The reaction mixture was allowed to warm up to rt and further stirred for 30 min. The reaction was quenched with water, the organic layer washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated.

Yield: 2.88 g, 98 %. Ms 522.3 $(M+H)^+$, Method ESI^+.

A suspension of the residue, 717 mg sodium azide (11.04 mmol) and 100 mg tetrabutylammonium iodide (0.27 mmol) in 10 ml DMF was stirred at 80°C for 20 hrs. The DMF was evaporated, the residue dissolved in ethyl acetate, washed with water and brine, the org. layer dried over Mg sulfate, filtered and the filtrate evaporated to dryness.

Yield: 2.5g, 97 %. MW:468.49, ($C_{23}H_{25}FN_6O_4$) MS: 469.7$(M+H)^+$, Method ESI^+.

4-[4-{(5S)-5-Aminomethyl-2-oxo-oxazolidin-3-yl}-2-fluoro-phenylamino]-piperidine-1-carboxylic acid benzyl ester.

A solution of 2,51 g (5.35 mmol) 4-[4-{(5R)-5-azidomethyl2-oxo-oxazolidin-3-yl}-2-fluoro-phenylamino]-piperidine-1-carboxylic acid benzyl ester, 1.54 g (5.88 mmol) triphenylphosphine and 964 µl (53.5 mmol) water in 30 ml THF was stirred at 50°C for 16h. The THF was evaporated. The residue was purified by chromatography using a dichloromethane/methanol 9/1 mixture with 1% ammonia.

Yield: 1.44 g, 78 %. MW:442.49, ($C_{23}H_{27}FN_4O_4$) MS: 443.6 $(M+H)^+$, Method ESI^+.

4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-piperidine-1-carboxylic acid benzyl ester.
A solution of 450 mg 4-[4-{(5S)-5-aminomethyl-2-oxo-oxazolidin-3-yl}-2-fluoro-phenylamino]-piperidine-1-carboxylic acid benzyl ester (1.01 mmol), 2 ml acetic acid and 0.093 ml (1 mmol) acetic anhydride was stirred at RT for 1 h. The solvents were evaporated.
Yield : 484 mg, quant. MW:484.53, ($C_{25}H_{29}FN_4O_5$) MS: 485.7 $(M+H)^+$, Method ESI^+.

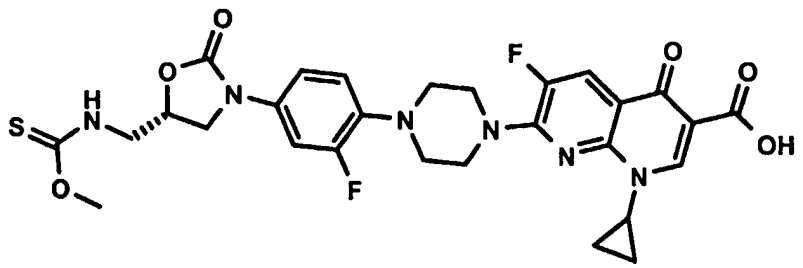
N-{(5S)-3-[3-Fluoro-4-(piperidin 4-ylamino)-phenyl]-2-oxo-oxazolidin-5-yl methyl}-acetamide.
A suspension of 480 mg (1 mmol) 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-piperidine-1-carboxylic acid benzyl ester and Pd/C in 2 ml of a methanol/ acetic acid 1/1 mixture was stirred under H_2 for 4h. The Pd/C was filtered and the filtrate was evaporated to dryness.
Yield: 350 mg, quant. MW:350.39, ($C_{17}H_{23}FN_4O_3$) MS: 351.6 $(M+H)^+$, Method ESI^+.

7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
A suspension of 100 mg N-{(5S)-3-[3-fluoro-4-(piperidin 4-ylamino)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}acetamide (0.28 mmol), 80.66 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (0.28 mmol) ,0.108 ml trimethylchlorosilane (0.84 mmol) and 0.16 ml triethylamine (1.12 mmol) in 2 ml DMSO was heated under stirring in a micro wave oven at 150 °C for 7 min. The DMSO was evaporated, the residue was purified by chromatography.
Yield: 54 mg, 31 %.MW:596.60, ($C_{29}H_{30}F_2N_6O_6$) MS: 597.5 $(M+H)^+$, Method ESI^+.

Known building blocks:

- 3,4-difluorobenzene: 369-34-6, Aldrich 28-836-5
- 4-Amino-N-benzylpiperidine : 50541-93-0, Acros 18766
- 1,8-Naphthyridine-3-carboxylic acid,7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-(9Cl): 100361-18-0, Louston International

EXAMPLE 24: 1-Cyclopropyl-6-fluoro-7-(4-{2-fluoro-4-[(5S)-5-(methoxythiocarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]-naphthyridine-3-carboxylic acid:



1-Cyclopropyl-6-fluoro-7-(4-{2-fluoro-4-[(5S)-5-(methoxy-thiocarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid.

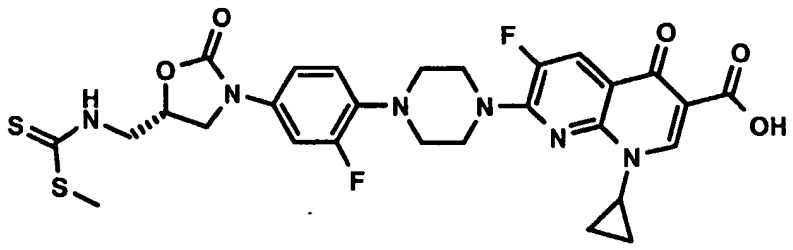
A mixture of 100 mg {[(5S)-3-[3-fluoro-(1-piperazinyl) phenyl]-2-oxo-5-oxalidinyl]methyl}-carbamothioic acid methyl ester (0.27 mmol), 76,71 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (0.27 mmol), 68,65 µl trimethylchlorosilane (0.54 mmol) and 113,49 µl triethylamine (0.81 mmol) in 3 ml acetonitrile was stirred in micro wave for 8 min at 150 °C. The reaction was diluted with water, and the precipitate was filtered and purified by chromatography using a dichloromethane / methanol 9/1 with 1% acetic acid.

Yield: 50 mg, 23 %.MW:614.63, ($C_{28}H_{28}F_2N_6O_6S$) MS: 615.2 $(M+H)^+$, 613.5 $(M-H)^-$, Method ESI^+, Method ESI^-.

Known buiding blocks:

- Carbamothioic acid,{[(5S)-3-[3-fluoro-(1-piperazinyl) phenyl]-2-oxo-5-oxalidinyl]methyl}-,o-methyl ester(9cl) :268208-73-7; WO 0027830
- 1,8-Naphthyridine-3-carboxylic acid, 7-chloro-1-cyclo-propyl-6-fluoro-1,4-dihydro-4-oxo-(9Cl):CAS 100361-18-0, Louston International

EXAMPLE 25: 1-Cyclopropyl-6-fluoro-7-(4-{2-fluoro-4-((5S)-5-(methylsulfanylthiocarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4dihydro-[1,8]naphthyridine-3-carboxylic acid:



4-{2-Fluoro-4-[(5S)-5-(methylsulfanylthiocarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester.

A mixture of 500 mg 1-piperazinecarboxylicacid,4-[4-[(5S)-5-[(acetylamino)methyl]2-oxo-3-oxazolidinyl]-2-fluoro-phenyl]-1,1-dimethylethyl ester, (1.26 mmol), 0.152 ml carbon disulfide (2.53 mmol) and 0.176 ml triethylamine (1.26 mmol) in 5 ml THF was stirred at 0°C for 7h. 79 µl methyliodide (1.26 mmol) was added dropwise to the reaction at 0°C, and the mixture was stirred at room temperature for 1h. The mixture diluted with

ethyl acetate and the org. layer was washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated.
Yield: 510 mg, 83 %. MW:484.61, (C21H29FN4O4S2) MS: 485.0 $(M+H)^+$, $)^-$, Method ESI^+.

[(5S)-3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-dithiocarbamic acid methyl ester.
A suspension of 510 mg 4-{2-fluoro-4-[(5S)-5-(methyl-sulfanylthiocarbonylamino-methyl)2-oxo-oxazolidin-3-yl]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester (1.05 mmol) in 1,25 M /methanol was stirred for 5 days. The solvent was evaporated and the residue digested in water. The water layer was neutralized at pH 7 with a saturated solution of sodium bicarbonate and evaporated to dryness .The residue was digested in CH_2Cl_2/MeOH. The salts were filtered and the solvent evaporated:
Yield: 250 mg, 25 %. MW:384.49, (C16H21FN4O2S2) MS: 385.5 $(M+H)^+$, Method ESI^+.

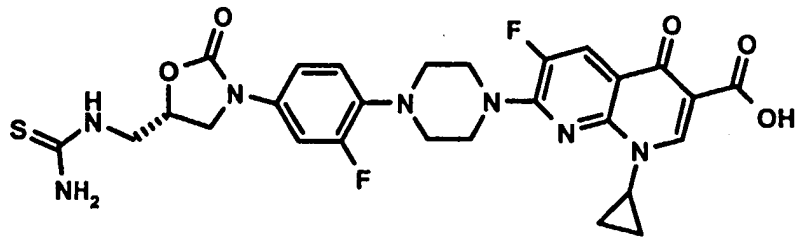
1-Cyclopropyl-6-fluoro-7-(4-{2-fluoro-4-((5S)-5-(methyl-sulfanylthiocarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4dihydro-[1,8]naphthyridine-3carboxylic acid
A mixture of 100 mg [(5S)-3-(3-fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-dithiocarbamic acid methyl ester (0.26 mmol), 73,51 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (0.26 mmol) 108µl triethylamine (0.78 mmol) and 65 µl trimethyl-chlorsilane (0.52 mmol), in acetonitrile was stirred in a micro wave oven for 8 min at 150°C. The solution was decanted from sticky solid, evaporated and the residue digested in water. The solid was

filtered and the purified by chromatography using a 9/1 dichloromethane/methanol mixture with 1 % acetic acid.
Yield:50 mg 30%.MW:630.70, ($C_{28}H_{28}F_2N_6O_5S_2$) MS: 631$(M+H)^+$

Known building blocks:

- 1-Piperazinecarboxylic acid,4-[4-[(5S)-5-[(acetylamino)-methyl]2-oxo-3-oxazolidinyl]-2-fluorophenyl]-,1,1-di-methylethyl ester,(S)-(9cl): 154990-65-5, US 5547950
- 1,8-Naphthyridine-3-carboxylic acid,7-chloro-1-cyclo-propyl-6-fluoro-1,4-dihydro-4-oxo-(9Cl):100361-18-0, Louston International

EXAMPLE 26: 1-Cyclopropyl-6-fluoro-{4-[2-fluoro-4-{(5S)-2-oxo-5-thioureidomethyl-oxazolidin-3-yl}-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



4-[2-Fluoro-4-{(5S)-2-oxo-5-thioureidomethyl-oxazolidin-3-yl}-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester
A suspension of 1g of 4-[2-fluoro-4-[(5R)-5-(isothio-cyanatomethyl)-2-oxo-3-oxazolidinyl]phenyl])-1-piperazine-carboxylic acid *tert*-butyl ester (2.29 mmol) in 5 ml methanol and 5 ml ammoniac 2N in ethanol was stirred at 0°C for 3 h. and at RT for 1 h. The precipitate was filtered and washed with ether.
Yield: 649 mg, 62 %. MW:453.53, ($C_{20}H_{28}FN_5O_4S$) MS: 454 $(M+H)^+$, Method ESI^+.

[(5S)-3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-thiourea.

A solution of 649 mg 4-[2-fluoro-4-{(5S)-2-oxo-5-thio-ureidomethyl-oxazolidin-3-yl}-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (1.43 mmol) in a mixture of 6 ml of a 1.25 M solution of hydrochloric acid in methanol and 1 drop water was stirred for 4 days. The solvent was evaporated, and the residue was neutralized at pH 7 with a saturated solution of sodium bicarbonate. The water was evaporated and the residue was digested in a 95/5 dichloromethane/methanol mixture and the solid filtered. The filtrate was purified by chromatography using a 95/5 dichloromethane/methanol mixture with 1% acetic acid.

Yield: 250 mg, 50 %. MW:353.42, ($C_{15}H_{20}FN_5O_2S$) MS: 354 $(M+H)^+$, Method ESI^+.

1-Cyclopropyl-6-fluoro-{4-[2-fluoro-4-{(5S)-2-oxo-5-thio-ureidomethyl-oxazolidin-3-yl}-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid.

A mixture of 100 mg [(5S)-3-(3-fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-thiourea (0.28 mmol), 87.98mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (0.31mmol), 71.57 µl trimethylchlorosilane (0.56 mmol) and 118,31 µl triethylamine (1.4 mmol) in acetonitrile was stirred in a micro wave oven for 8 min at 150 °C. The reaction mixture was diluted with water and the solid filtered. The solid was purified by chromatography using a 95/5 dichloromethane / methanol mixture with 1% acetic acid as eluent to leave 50 mg of an oily residue which was crystallized from a ETOAC/hexane mixture.

Yield: 30 mg, 17 %. MW:599.62, ($C_{27}H_{27}F_2N_7O_5S$) MS: 600 $(M+H)^+$, Method ESI^+.

Known building blocks:

- 1-piperazinecarboxylic acid, 4-[2-fluoro-4-[(5R)-5-(isothiocyanatomethyl)-2-oxo-3-oxazolidinyl]phenyl]-,1,1-dimethylester(9cl): WO 0027830
- 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid:100361-18-0 ,Louston International

All examples were tested against several gram positive and gram negative bacteria. They all have a broader and more pronounced activity than the corresponding quinolone and oxazolidinone as well as a 1+1 combination of these two compounds.

Typical MIC range (mg/l)

S. aureus (MRSA): 0.125-2 (linezolid : 1-2, ciprofloxacin: 0.5-32)

S. aureus (MSSA): 0.06-1 (linezolid : 1-2, ciprofloxacin: 0.125-1)

E. faecalis =<0.03-1 (linezolid : 0.5-2, ciprofloxacin: 0.5-32)

E. faecium =<0.03-1 (linezolid : 1-2), ciprofloxacin: 0.25-32)

S. pneumoniae =<0.03-1 (linezolid: 0.125-1), ciprofloxacin: 1-4)

EXAMPLE 27: 7-(4-{4-[5(S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:

A mixture of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylate (80 mg), (S)-N-[[3-(3-fluoro-4-(4-piperidinyloxy)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (described WO2001046164; 100mg), triethylamine (120 microL) and

trimethylchlorsilane (72 microL) in DMSO (2 mL) were stirred at 150°C for 5 minutes (microwave). The solvent was evaporated and the crude reaction was taken up with water. The resulting solid was filtered and chromatographed over silicagel (dichloromethane/methanol 95:5). The interesting fractions were collected and recrystallised from ethyl acetate /n hexane affording 70 mg (41%) of colorless material.

$C_{29}H_{29}F_2N_5O_7$ (597.58)
MS: 598.5 (M+H); 596.4 (M-H).

EXAMPLE 28: 7-(4-{4-[5(S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:
A mixture of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylate boron diacetate (described in WO8807998; 175 mg, 0.42 mmol(S)-N-[[3-(3-fluoro-4-(4-piperidinyloxy)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (150mg, 0.42 mmol) and DABCO (47 mg, 0.42 mmol) were stirred at 150°C in 2 ml DMSO for 7 minutes (microwave). The solvent was evaporated and the crude reaction was taken up with water. The resulting solid was filtered and chromatographed over silicagel (dichloromethane/methanol 95:5). The interesting fractions were collected and crystallised from acetonitrile affording 23 mg (9%) of colorless material.

$C_{30}H_{30}F_2N_4O_7$ (596.59)
MS: 597.5 (M+H).

EXAMPLE 29: 7-(4-{4-[5(S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylsulfanyl}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:

Was prepared in analogy to example 28 starting from 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylate boron diacetate and(S)-N-[[3-(3-fluoro-4-(4-piperidinylsulfanyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. The later being obtained from 4-mercapto-piperidine-1-carboxylic acid tert-butyl ester (J. Antibiotics, 1995, 48, 408-16)

$C_{30}H_{30}F_2N_4O_{6S}$ (612.66)

MS: 613.8 $(M+H)^+$.

EXAMPLE 30: 7-(4-{4-[5(S)-5(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylsulfanyl}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:

Was prepared in analogy to example 27 starting from 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylate and(S)-N-[[3-(3-fluoro-4-(4-piperidinylsulfanyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

$C_{29}H_{29}F_2N_5O_{6S}$ (612.66)

MS: 613.8 (M+H).

It has been found that compounds according to the present invention exhibit an improved action for the prevention, alleviation or treatment of diseases in the human or animal body. The reasons for the improved action are not yet completely understood. One reason might be that pathogenic organisms have

defense mechanisms wherein different medicaments are neutralised by different means (active efflux, metabolic transformation or mutation(s) in the target.

The compounds of the present invention might no more be substrates for the various enzymes or receptors in charge of the detoxification of the bacteria. Further resistance through simultaneous mutation in the active sites of the two targets is unlikely or very difficult.

Claims

1. Compound which contains at least two pharmaceutically active components.

2. Compound according to claim 1 wherein at least one pharmaceutically active component is a therapeutically active component.

3. Compound according to any one of the preceding claims wherein at least two components share at least one structural element.

4. Compound according to any one of claims 1 to 3 wherein at least two components are connected with a covalent bond.

5. Compound according to any one of claims 1 to 3 wherein at least two components are connected with a spacer.

6. Compound according to any one of the preceding claims wherein the structural element, the covalent bond and/or the spacer is stable under physiological conditions.

7. Compound according to any one of the preceding claims wherein at least two components have different pharmaceutical and/or therapeutical effects.

8. Compound according to any one of the preceding claims wherein at least two components have the same pharmaceutical and/or therapeutical effect.

9. Compound according to any one of the preceding claims wherein all components have different pharmaceutical and/or therapeutical effects.

10. Compound according to any one of the preceding claims wherein all components have the same pharmaceutical and/or therapeutical effect.

11. Compound according to any one of the preceding claims wherein at least one therapeutically active component has antibiotic activity.

12. Compound according to any one of the preceding claims wherein at least two therapeutically active components have antibiotic activities.

13. Compound according to any one of the preceding claims wherein all therapeutically active components have antibiotic activities.

14. Pharmaceutical compositions which contain a compound according to any one of the preceding claims and optionally carriers, adjuvants and/or diluents.

15. Use of a compound or pharmaceutical composition according to any one of the preceding claims for the preparation of a medicament for the treatment or prevention of bacterial infections.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/10765

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/12 C07D498/04 C07D413/14 C07D471/04 A61K31/496
A61K31/5383 A61K31/4709 A61K31/5395 A61K31/4375 A61K31/4545
A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 196 01 265 A (BAYER AG) 17 July 1997 (1997-07-17) page 1 Examples ---	1-15
X	WO 93 09103 A (UPJOHN CO) 13 May 1993 (1993-05-13) page 3 -page 7 examples 34-36,45-47 ---	1-15
X	PATENT ABSTRACTS OF JAPAN vol. 014, no. 250 (C-0723), 29 May 1990 (1990-05-29) & JP 02 069478 A (SAGAMI CHEM RES CENTER;OTHERS: 01), 8 March 1990 (1990-03-08) abstract --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 January 2003	05/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hornich, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/10765

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 491 139 A (WHITE RONALD E ET AL) 13 February 1996 (1996-02-13) abstract column 1, line 1 - line 32 col. 4, 'Quinolonyl Lactams'; col. 9, 'Lactam-containing Moieties'; col. 21, 'Quinolone Moieties'; col. 33, 'Linking Moieties'	1-15
A	EP 0 266 576 A (BRISTOL MYERS CO) 11 May 1988 (1988-05-11) abstract page 2 -page 9	1-15
A	EP 0 390 215 A (WAKUNAGA SEIYAKU KK) 3 October 1990 (1990-10-03) abstract page 3 -page 4, line 20 in particular l. 32,33,43 page 5	1-15
A	US 5 221 676 A (LABORDE EDGARDO ET AL) 22 June 1993 (1993-06-22) abstract column 1, line 15 - line 58 column 3, line 37 - line 45	1-15
P,X	WO 02 059116 A (BARBACHYN MICHAEL R ;GORDEEV MIKHAIL F (US); UPJOHN CO (US); GAGE) 1 August 2002 (2002-08-01) abstract page 1 -page 2 page 4 page 5, line 12 -page 7, line 15 in particular p. 6, l. 17/18 p. 14, 'preferred compounds' p. 15, compounds 3 and 6 page 17, line 4 - line 6 page 25, line 1 - line 32 examples 1,2 claims 1,12,13,26-28	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/10765

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-15 relate to an extremely large number of possible compounds.
Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Consequently, the search has been carried out for those parts of the application which do appear to be supported and disclosed, namely the compounds encompassed by the Markush-Formula in particular with respect to the examples given in the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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